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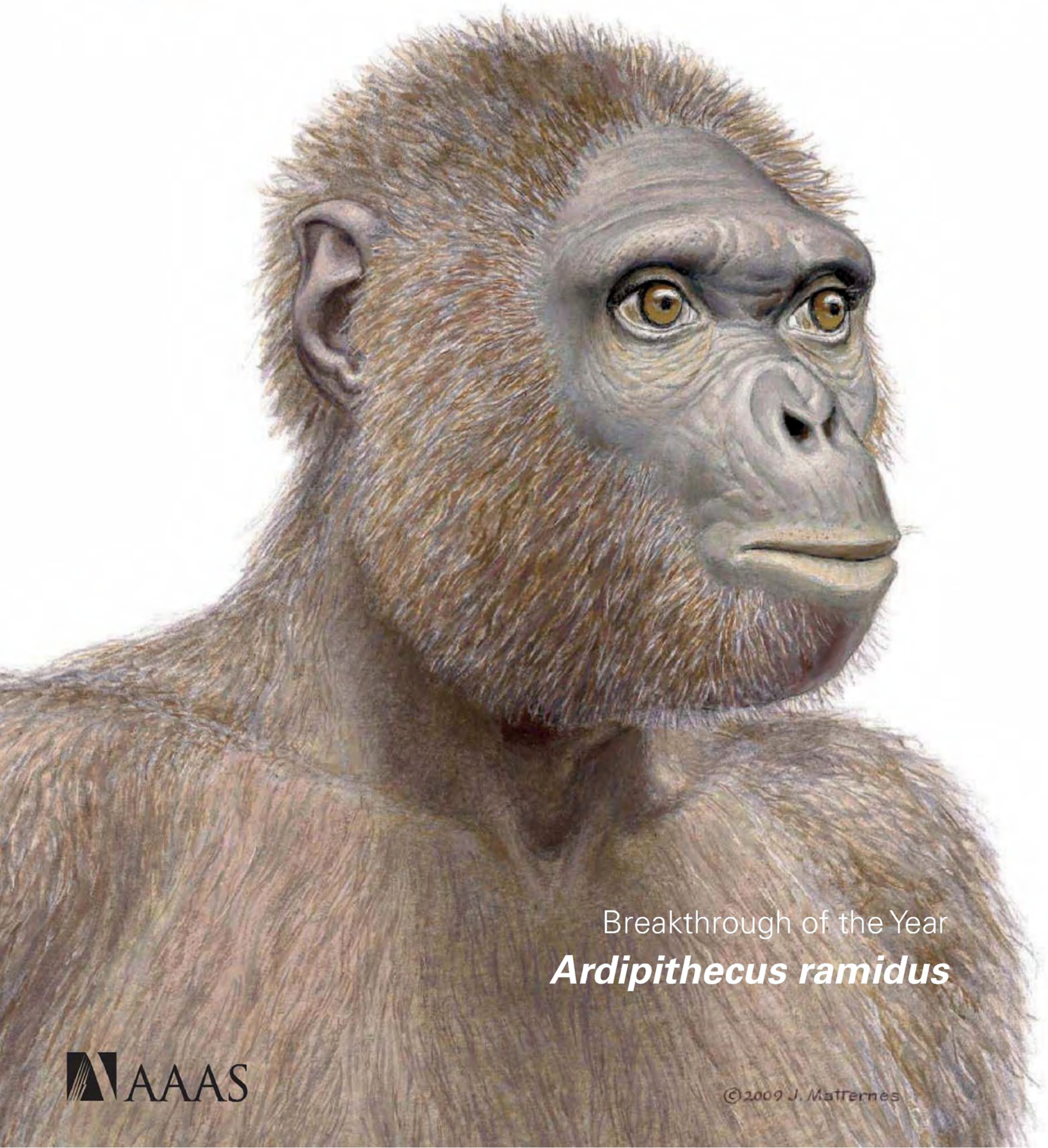

Breakthrough of the Year

Ardipithecus ramidus

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Breakthrough of the Year

WINNER

RUNNERS-UP

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>> Editorial p. 1589; Science Podcast; for related online content, go to www.sciencemag.org/btoy2009/

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EDITORIAL

NEWS OF THE WEEK

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EDUCATION FORUM

PERSPECTIVES

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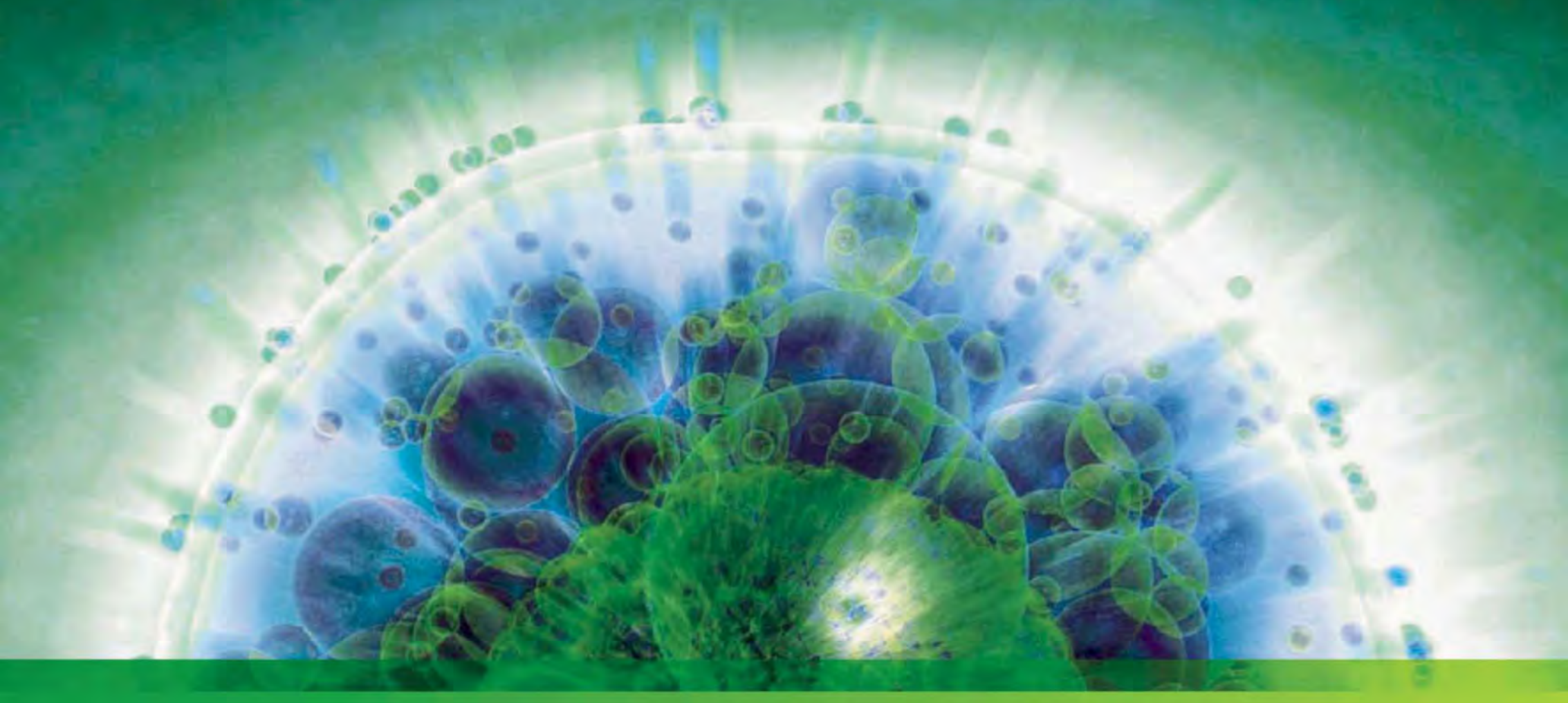
COVER

Ardipithecus ramidus, a possible human ancestor, inhabited then-wooded regions of Ethiopia 4.4 million years ago. This year, studies of the fossilized skeleton of a member of the species raised surprising questions about how key human traits evolved. See the Breakthrough of the Year special section beginning on page 1598 and at www.sciencemag.org/btoy2009/.

Image: © 2009, Jay Matternes

DEPARTMENTS

A New Era in the Study of Stem Cell Pluripotency



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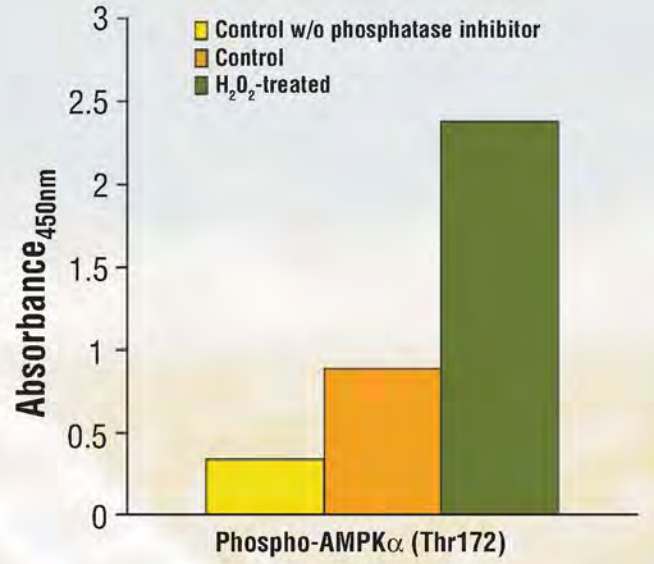

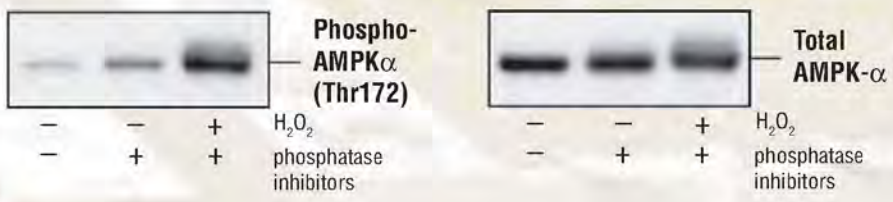

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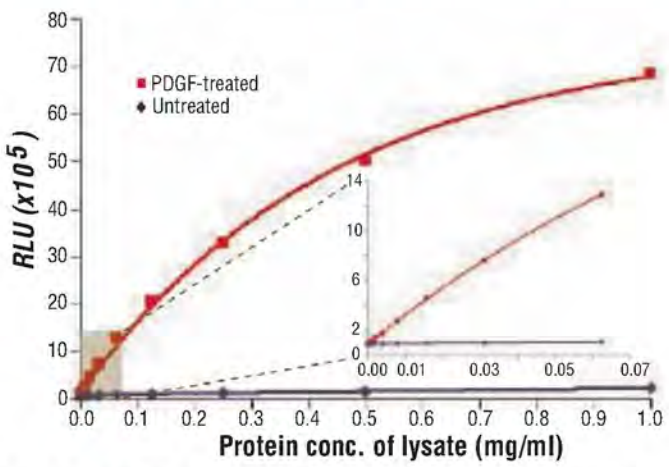

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Spontaneous- and X-ray–Triggered Crystallization at Long Range in Self-Assembling Filament Networks
H. Cui et al.

Dilute solutions of alkyl-terminated peptide filaments can undergo ordering upon x-ray exposure.
10.1126/science.1182340

Objective Confirmation of Subjective Measures of Human Well-Being: Evidence from the U.S.A.
A. J. Oswald and S. Wu

Subjective life-satisfaction scores agree with objective measures of well-being across 50 American states.
10.1126/science.1180606

p53 Controls Radiation-Induced Gastrointestinal Syndrome in Mice Independent of Apoptosis
D. G. Kirsch et al.

Ionizing radiation destroys gastrointestinal epithelial cells by a mechanism that appears to be independent of apoptosis.
10.1126/science.1166202

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HIV Outwits Yet Another Microbicide
Failure marks the end of the road for nonspecific virus blockers.

A Mind That Touches the Past
People with a sensory mix-up also have exceptional memories.

A Cheap Way to Chop Up Nitrogen
New chemical reaction allows conversion of the ubiquitous gas into a common fertilizer.

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RESEARCH ARTICLE: EGFR Signaling Through an Akt-SREBP-1–Dependent, Rapamycin-Resistant Pathway Sensitizes Glioblastomas to Antilipogenic Therapy
D. Guo et al.

Inhibitors of fatty acid signaling promote apoptosis in glioblastoma cells with highly active EGFR signaling.

RESEARCH ARTICLE: Function of the Nucleotide Exchange Activity of Vav1 in T Cell Development and Activation
A. Saveliev et al.

The guanine nucleotide exchange activity of Vav1 is required for some, but not all, of its functions in T cells.

PERSPECTIVE: Cell Mechanics and Feedback Regulation of Actomyosin Networks
R. Fernandez-Gonzalez and J. A. Zallen

Mechanical signals shape the organization and dynamics of contractile networks in cells during morphogenesis.

PERSPECTIVE: Book Review—Making Sense of Signal Transduction
W. T. Miller

A textbook provides an overview of signaling concepts and models for teaching.

PODCAST
P. S. Mischel and A. M. VanHook

Inhibiting fatty acid synthesis may be effective in controlling glioblastomas driven by EGFR signaling.

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Tooling Up: Presenting Your Technology
D. Jensen

Budding scientist-entrepreneurs must be able to present their company skillfully to potential investors and partners.

Breakthrough of the Year: A Tale of Two Paleontologists
E. Pain

Two young paleontologists tell how they got involved in the field work that uncovered *Ardipithecus ramidus* in Ethiopia.
>> Breakthrough of the Year section p. 1598 and www.sciencemag.org/btoy2009/

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PERSPECTIVE: Pharmacologic Induction of CD8$^+$ T Cell Memory—Better Living Through Chemistry
L. Gattinoni et al.

Targeting the immune system using small molecules may enhance immunotherapy.

PERSPECTIVE: Toward a Systems-Level Analysis of Infection Biology—A New Method for Conducting Genetic Screens in Human Cells
S. A. Stanley and D. T. Hung

Human genetic screens at the DNA level advance therapeutic development.

RESEARCH ARTICLE: Intravenous Hemostat—Nanotechnology to Halt Bleeding
J. P. Bertram et al.

Bioengineers develop functional blood cells.

SCIENCESIGNALING
Structure of Vav1.

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See an expanded version of this week's special section, with references, links, and multimedia at **www.sciencemag.org/btoy2009/**.

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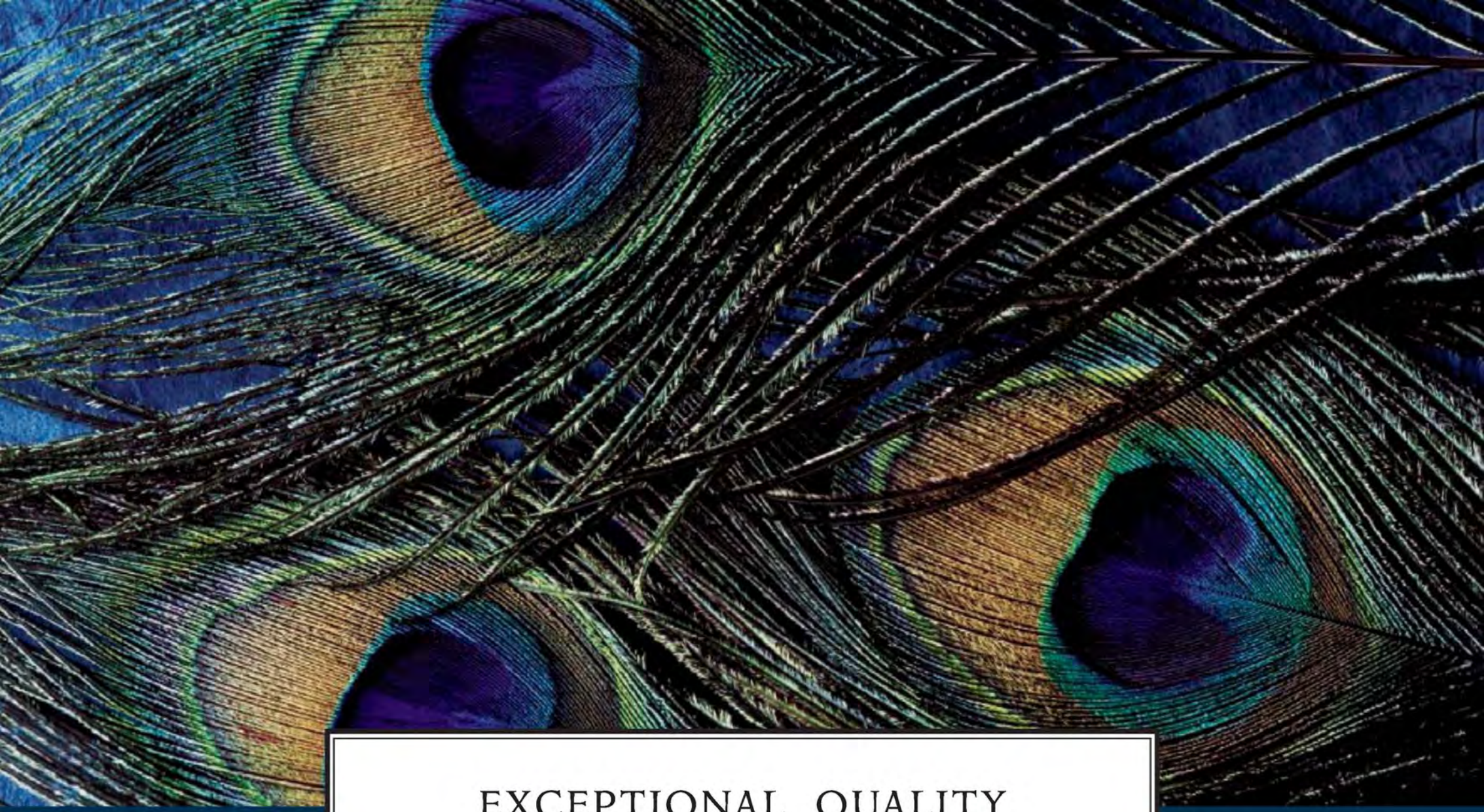

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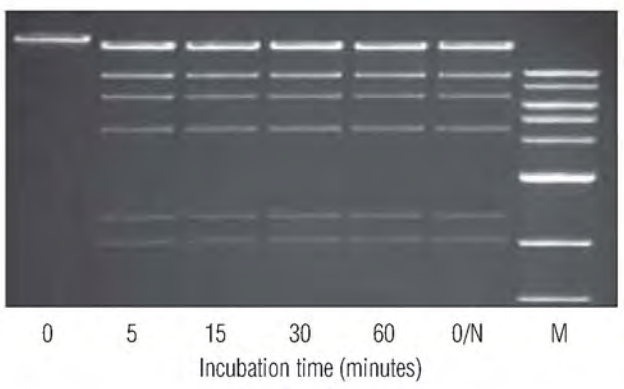

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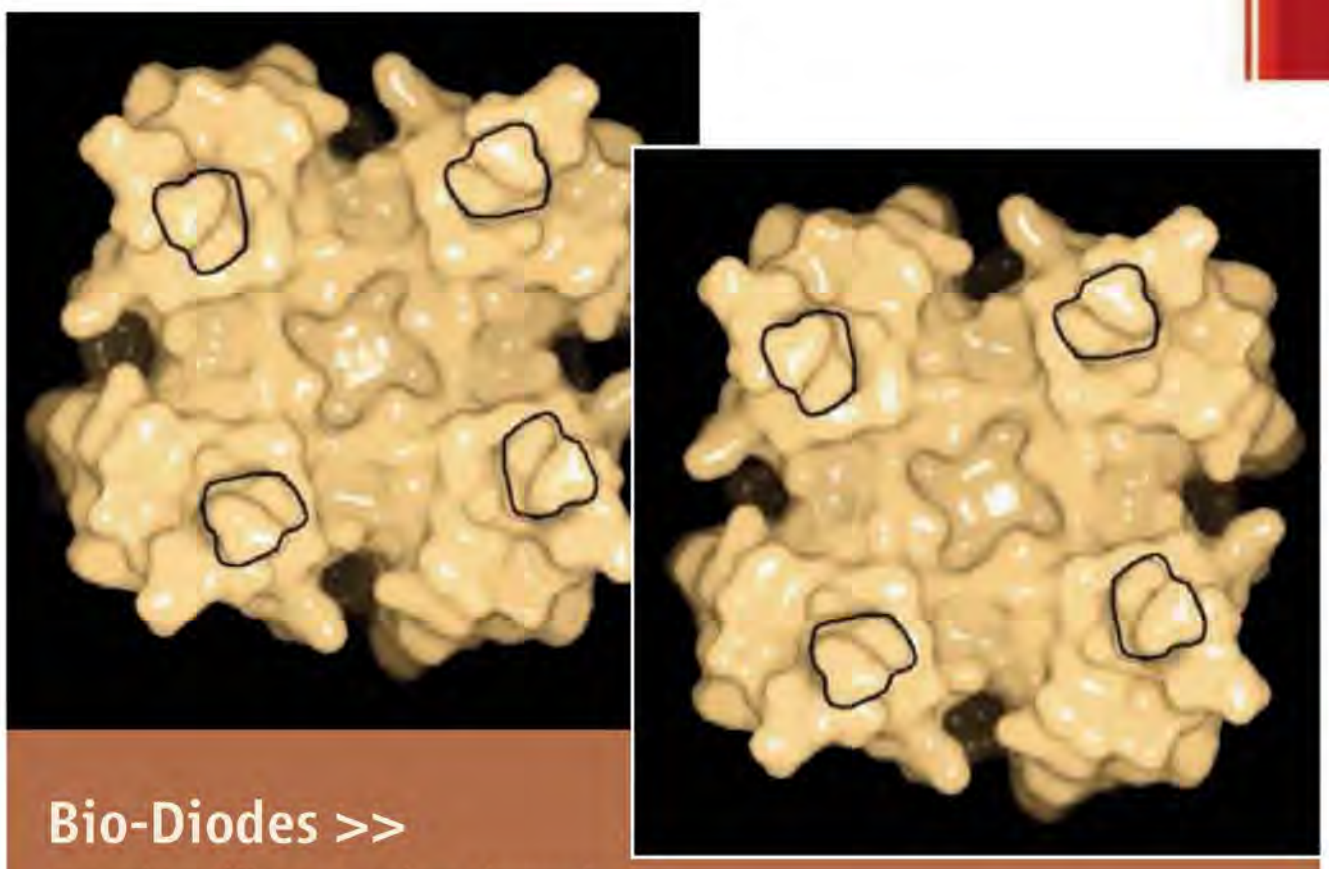


Bio-Diodes >>

Inward rectifier potassium channels conduct K^+ ions into the cell at internal negative membrane voltages, but at internal positive membrane voltages they are blocked by intracellular multivalent ions. These channels control the resting membrane voltage and are required for the healthy function of many electrically excitable cells. Mutations can result in transient paralysis causing, for example, heart problems. **Tao *et al.*** (p. 1668) now report a 3.1 angstrom resolution structure of the inward rectifier, Kir2.2 from chicken, which has a similar structure to the human equivalent. The combination of observations of conductive and inhibitory ion binding sites with electrophysiological data finally explains the mechanism of action of these long-studied channels and reveals how they maintain their low sensitivity to toxins, as well as provides a basis for the design of therapeutic drugs.

Seed for Food

The seeds of grain-producing plants are more difficult to harvest than nuts or fruits as food. It has been unclear when early humans began to rely extensively on grains, but **Mercader** (p. 1680) has discovered films of starch residues on stone tools at a cave site in Mozambique dating to about 100,000 years ago. The residues are consistent with starch grains from wild sorghum and indicate that early humans relied on cereals much earlier than previously thought. The Mozambican example of sorghum exploitation thus represents the longest known tradition of cereal use in the world.

Moving Boundaries

Classical models of fine-grained metals view grain boundaries as static objects, but this view has been challenged by recent experimental observations. Drawing on techniques used by the fracture mechanics community, **Rupert *et al.*** (p. 1686) present experiments on freestanding aluminum films that show specific geometries cause either stress or strain concentrations on

deformation. Confirming recent simulations, shear stresses were found to be a key driver of grain boundary motion.

Degrees of Darkness

Fruit flies in Africa have a tendency to be darker, the higher the altitude at which they live, because melanization offers a selective advantage. The dark pigmentation seen in some populations of Ugandan *Drosophila melanogaster* is owing to a lack of expression of the *ebony* gene, and expression results in yellow cuticle. **Rebeiz *et al.*** (p. 1663; see the News story by **Pennisi**) show that mutations in *cis* regulatory elements, rather than in the coding region, are responsible for the dark color. A series of five mutations in a modular enhancer element influences the level of *ebony* expression: Three mutations already existed in fly populations with light cuticle color and a further two, more recently acquired dark-specific substitutions, together have created an allele of large effect, which has been swept to high frequency in this population of flies.

Watery Worlds

Water vapor has been detected in the protoplanetary disks of a variety of stars. Explaining its origin is important because it bears on our understanding of planet formation. **Bethell and Bergin** (p. 1675) propose that this water originates in photochemistry occurring in the upper layers of the disks. In these regions, the rate at which water is produced exceeds the rate at which water is destroyed by ultraviolet radiation. Water forming in the upper layers of the disks then shields water vapor within the disks' interiors, allowing that vapor to interact with planet-forming materials and possibly be incorporated into young planets.

Home Is Where the Hearth Is

One aspect of human intelligence is the ability to organize our living and working spaces. It was generally thought that this capability arose with modern humans in the past 100,000 years or so. However, **Alperson-Afil *et al.*** (p. 1677) found evidence of domestic organization 800,000 years ago at a Pleistocene hominin campsite in the Jordan Valley. Around patches of burnt debris, the remains of a wide range of plant and animal foodstuffs were found, including fruits and seeds, as well as remnants of turtles, elephants, and small rodents. Specific types of stone tools appear to have been made around the hearths, where there was also evidence of nut roasting and consumption of crabs and fish. In a more distant area there were signs of intensive flint knapping and food chopping.

A Glimpse of Wet Carbonic Acid

Both carbon dioxide and bicarbonate play extraordinarily widespread roles in biochemical and geochemical reactions. It is surprising therefore that carbonic acid, the intermediate in the water-coupled interconversion of these two compounds, has never been directly characterized in aqueous solution. **Adamczyk *et al.*** (p. 1690, published online 12 November) have succeeded in glimpsing the elusive acid by inducing an aqueous photoacid (a compound rendered tran-

Continued on page 1588

CREDITS (TOP TO BOTTOM): TAO *ET AL.*; RUPERT *ET AL.*

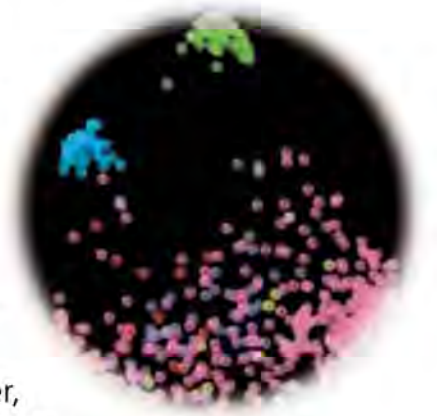
Continued from page 1587

siently more acidic upon light absorption) to react with dissolved bicarbonate. Using infrared spectroscopy, they show that the carbonic acid product persists for nanoseconds. Analysis of its formation kinetics affords a direct pK_a value of 3.5, substantially lower than the effective value derived from observations of the net bicarbonate/carbon dioxide equilibrium.

Fanconi Cross-Links

Fanconi anemia is a rare genetic disease characterized by bone marrow failure, developmental abnormalities, and dramatically increased cancer susceptibility. Cells derived from Fanconi anemia patients are sensitive to agents that cause DNA interstrand cross-links, indicating that under normal circumstances the Fanconi pathway controls the repair of these DNA lesions. **Knipscheer *et al.*** (p. 1698, published online 12 November) found that two Fanconi anemia proteins, FANCI and FANCD2, promoted the DNA replication–coupled repair of interstrand cross-links in cell extracts. The FANCI-FANCD2 complex was required for the incisions that unhook the cross-link and for the insertion of a nucleotide across from the damaged template base during lesion bypass.

Growing on You



The human gut and skin harbor diverse microbial communities that are known to vary strikingly among individuals. Here, **Costello *et al.*** (p. 1694, published online 5 November) analyzed microbial diversity among several distinct body habitats (including the gut, mouth, inside the ears and nose, and skin) of the same person at different times. They found that body habitat had more influence on microbial community composition than temporal differences and variation among people. Some skin locations, such as the index finger, back of the knee, and sole of the foot, on occasion harbored higher microbial diversity than the gut or oral cavity.

Cheaper Cooperation

In the context of public goods games in which optimal benefit is achieved when all participants contribute, bad behavior cannot always be deterred by direct punishment, and has the added disadvantage that the punisher may suffer a cost. Alternatively, instead of punishment, rewarding those who contribute can be effective in encouraging and maintaining widespread cooperation, with the added plus that group benefits are not diminished by the costs of punishment. But **Ule *et al.*** (p. 1701) discovered experimentally that if someone is treated depending on how they have behaved in previous interactions, retaining the option to occasionally apply punishment shifts the payouts to favor cooperators more than defectors.

Local Selection of Magic Traits

Ecological interactions can favor specialization, and sexual selection can induce reproductive isolation; however, these processes are insufficient by themselves to create new species. They must act in concert and on the same set of genes. **Van Doorn *et al.*** (p. 1704, published online 26 November; see the Perspective by **Mank**) present a theoretical model that shows that within a larger population the evolution of mating preferences will favor sexual ornaments that indicate the degree of adaptation to the local ecological conditions, for example, the abundant song of a male bird that can obtain food easily because it has the right bill size for the seeds in that locale. Once mate choice evolves on the basis of a signal of local adaptation, natural and sexual selection will mutually enforce each other, ultimately leading to speciation.

Silent Hate

A great deal of information can be communicated nonverbally. **Weisbuch *et al.*** (p. 1711; see the Perspective by **Dovidio**) have used experimental, archival, and survey studies to find that the nonverbal communication of racial bias in popular television shows perpetuates implicit racism in viewers. A subsequent field data analysis yielded a correlation between U.S. viewer ratings and a Federal Bureau of Investigation tally of anti-black hate crimes in the same localities.

CREDIT: COSTELLO *ET AL.*

Bruce Alberts is Editor-in-Chief of *Science*.

The Breakthroughs of 2009

EVERY DECEMBER, THE EDITORS OF *SCIENCE* FACE THE CHALLENGE OF REVIEWING WHAT SCIENCE HAS accomplished around the world in the past 12 months, so as to select our "breakthroughs of the year." The task is an invigorating one, providing a powerful reminder of both the enormous scope and the continual advance of science. For this year's selections, the range is staggering. From the discovery of pulsars created by neutron stars that are many thousands of light-years distant, to the production of a new single-atom–thick material such as graphene, the same natural laws and logic have generated new understandings over a more than 10^{30}-fold difference in scale. And there is usually special excitement when an advance directly concerns humans, as in the discovery of an ancient ancestor or a successful application of gene therapy to cure disease.

This year's selection for the Breakthrough of the Year is the reconstruction of the 4.4-million-year-old *Ardipithecus ramidus* skeleton and her environs, published in *Science* as a major series of 11 articles in October. This choice does not come easily, given the distaste of our editors for self-promotion. But this work changes the way we think about early human evolution, and it represents the culmination of 15 years of highly collaborative research. Remarkably, 47 scientists of diverse expertise from nine nations joined in a painstaking analysis of the 150,000 specimens of fossilized animals and plants [see *Science* **326**, 62 (2009) for photos and locations of each author].

The 11 *Ardipithecus* papers, requiring 89 pages of text plus 295 pages of supporting online material, provide an enormous amount of data for scientists around the world to reexamine. As described on p. 1598 in the current issue, some of those scientists are certain to challenge some of the findings, as further advances are built on those already published. With time, we will come to understand much more, and some current conclusions will probably be modified. This is both to be expected and hoped for: Science can only advance as a highly collaborative global endeavor, through which new knowledge improves on old knowledge based on logic and confirmable evidence.

Our Runner-Up Breakthrough of the Year is "opening up the gamma-ray sky," as represented by the discovery of gamma-ray pulsars with the Fermi Gamma-ray Space Telescope. Astrophysicist Michael Turner, a member of our Senior Editorial Board, emphasizes the telescope's astounding capability to scan the entire sky in less than 3 hours, with a sensitivity orders of magnitude better than its predecessors, superior angular resolution and energy coverage, and time coverage ranging from milliseconds to months. The Fermi Telescope has thereby revealed, with unprecedented detail, a very restless high-energy universe, and it is solving old mysteries while making new, unexpected discoveries.

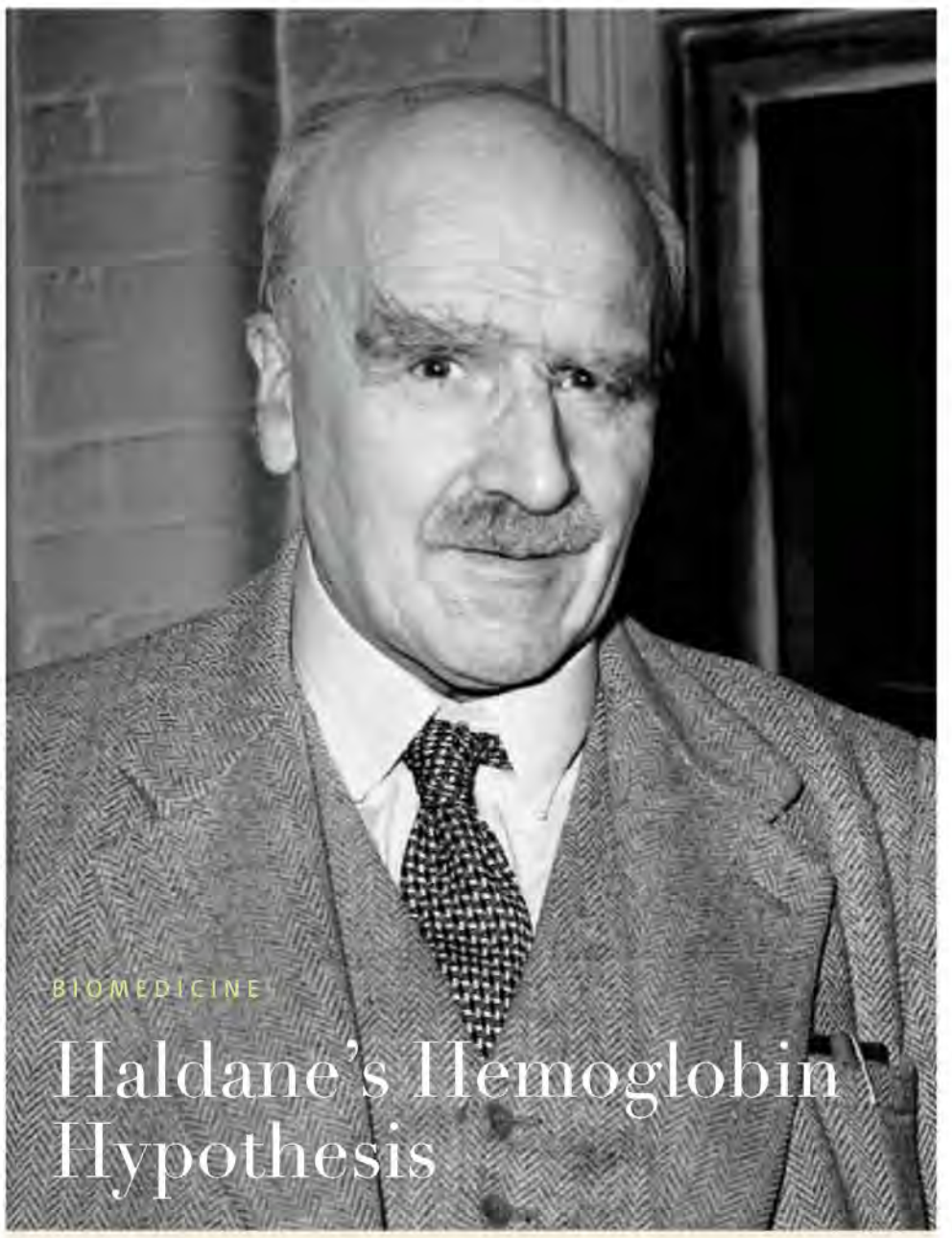
A glance at the remaining eight breakthroughs on our list similarly reveals a heavy dependence of new science on remarkable engineering feats. Most obvious are the Hubble Telescope repair and the giant x-ray laser created at the Stanford Linear Accelerator. But it would be hard to overestimate the benefits to modern science from the development of sophisticated new technologies in essentially every discipline. Indeed, new understandings of the natural world derived from science are constantly being used to generate new techniques and instruments that greatly speed the next scientific discoveries, helping to explain the accelerating pace at which science advances.

To take an example from my field of biology, advances in the techniques for sequencing DNA will soon have moved us from a $3 billion human genome to a $3000 human genome in less than 20 years—a reduction in cost of a million-fold, attributable to collaborations of scientists with engineers.

Today, more than ever, scientists and engineers across the globe need each other if we are to continue to achieve the remarkable advances in human understanding that we celebrate in *Science*'s final issue every year: the kind of breakthroughs that the world will always require to improve the welfare of human beings.

– Bruce Alberts

10.1126/science.1185821



BIOMEDICINE

Haldane's Hemoglobin Hypothesis

Malaria parasites invade and feed within human red blood cells and can cause high rates of mortality if untreated. Consequently, and as hypothesized by Haldane, in recent human history malaria has selected for several hemoglobin mutations with distinctive patterns of global distribution, which hinder the parasite to different degrees. Penman *et al.* have investigated the population genetics of the contrasting distributions of hemoglobin mutations associated with thalassemias (which exhibit quantitative deficiencies in α- and β-globin synthesis that can provide up to 60% protection against malaria) in the Mediterranean, and those of sickle-cell anemia (a structural defect in β-globin that confers in excess of 90% malaria protection) in sub-Saharan Africa. The authors suggest that the distinct geographies reflect an active exclusion of the sickle-cell mutation from Mediterranean populations as a result of intracellular interactions between the α- and β-globin variants. The pathophysiology of the thalassemias is caused by an imbalance in the globin subunits; several mutations coexist, and if an individual inherits two different thalassemia mutations, the imbalance may be ameliorated without any loss of the malaria-protective effect. In contrast, co-inheritance of an α thalassemia with sickle cell anemia ablates any malaria-protective effect and transmits a double whammy of hemoglobinopathy and malaria risk to the afflicted individual. — CA

Proc. Natl. Acad. Sci. U.S.A. 10.1073/pnas.0910840106 (2009).

CELL BIOLOGY

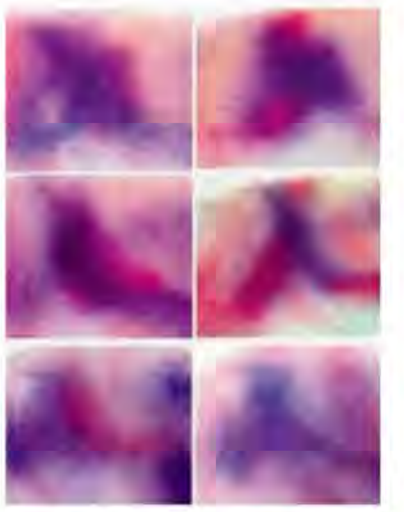
A Message in a Vesicle

When cells undergo programmed cell death, small portions of the plasma membrane pinch off and form microvesicles known as apoptotic bodies. Zernecke *et al.* show that apopototic bodies carry a message from the dying cells to healthy ones that promotes the repair of atherosclerotic lesions. Apoptotic bodies from dying human umbilical vein endothelial cells were taken up by healthy endothelial cells and increased expression of the gene encoding CXCL12, a chemokine that recruits progenitor cells to sites of repair. The active component of the apoptotic bodies was not a protein but the microRNA miR-126, which inhibited the translation of the mRNA encoding an inhibitor of signaling via CXCR4, which is the receptor for CXCL12 and also enhances its expression. In a mouse model of atherosclerosis, administration of apoptotic bodies or miR-126 promoted the production of CXCL12 and reduced the size of lesions in the blood vessels. — LBR

Sci. Sig. **2**, ra81 (2009).

DEVELOPMENT

Bounded Excitement



Glutamatergic neurons (red) in the caudal thalamus.

CREDITS (TOP TO BOTTOM): NEWSCOM; SCHOLPP *ET AL., PROC. NATL. ACAD. SCI. U.S.A.* **106**, 19895 (2009)

Brain development is characterized by shifting patterns of gene expression and by gradients of cell differentiation. Scholpp *et al.* have analyzed the zebrafish thalamus to understand how one such gradient defines neuronal phenotype. Proteins of the Hes/Her family repress transcription of their target genes, which in some cases keeps a neural progenitor cell in its precursor state. Initially, *her6* is expressed throughout the developing thalamic region. Cells in the rostral thalamus, which maintain *her6* expression longer, normally develop into inhibitory GABAergic neurons, whereas cells in the caudal thalamus, from which *her6* expression recedes earlier, begin to express *neurog1* and develop into excitatory glutamatergic neurons. Overly persistent expression of *her6* in the caudal thalamus suppresses *neurog1* and induces those cells to develop into GABAergic neurons. Thus, the shifting pattern of *her6* expression defines separate identities for these two thalamic regions. — PJH

Proc. Natl. Acad. Sci. U.S.A. **106**, 19895 (2009).

EDUCATION

Elementary Partnership

The Elementary Science Education Partnership (ESEP) was created to bring elementary school teachers into working partnerships with science-literate college students, who would carry their knowledge, confidence, and enthusiasm for science into the teachers' classrooms. Goebel *et al.* report the implementation and preliminary impact of the program. ESEP hired experienced educators and administrators to guide the professional development of the classroom teacher mentors, including instruction at summer institutes in both the science content and pedagogical strategies required to teach a science kit. These teacher mentors, called SKIL teachers, went on to train their colleagues at their home schools. Undergraduates completed a one-semester course where they learned inquiry-based approaches to science learning and

science pedagogy. For one semester, undergraduate and teacher pairs committed 3 to 4 hours per week to hands-on activity in the classroom. It became an honor among teachers and administrators to be chosen to participate in the program. Evaluation showed that teachers mentored by SKIL teachers were better able to design and implement lessons and were more capable of conveying scientific subject matter than those who were not mentored. Undergraduates also reported gains in their own understanding of science as a result of having taught basic elements. — MM

CBE Life Sci. Edu. **8**, 239 (2009).

PHYSICS

Racing Down the Table

Accelerating particles to very high energy is usually done at large national facilities with the aim of smashing atoms to probe their constituent parts. Accelerators on a smaller, but still rather grand, size scale find use in biomedical applications such as cancer treatment. The availability of high-intensity laser pulses to manipulate electrons offers the possibility of shrinking the size of particle accelerators even further. However, the demonstrations of laser-based acceleration so far have been at large laser facilities and have involved pulses produced at a low repetition rate. Mordovanakis *et al.* report a technique to produce electrons at faster repetition rates, using a double pulse setup whereby a moderate prepulse (~10^{14} W cm^{-2}) is focused onto a target before the arrival of the main pulse (10^{18} W cm^{-2}). By varying the delay time between the prepulse and the main pulse, the authors can control the 500-Hz production of quasi-monoenergetic electron pulses at relativistic energies (0.8 MeV), thereby offering the prospect of tabletop accelerators. — ISO

Phys. Rev. Lett. **103**, 235001 (2009).

BIOCHEMISTRY

Cobalt Ins and Outs

Vitamin B_{12} (cobalamin) has been cited prominently in the history of the Nobel Prizes, for its contributions to pernicious anemia, organic synthesis, and crystallography. Methylmalonyl-CoA mutase (MCM) is one of only two mammalian enzymes that rely on cobalamin, and Padovani and Banerjee describe the intricate mechanisms for ensuring that active cofactor is loaded onto MCM and inactive cofactor is removed. A trimeric adenosyltransferase (ATR) turns inactive cobalamin into the active AdoCbl form by adding the deoxyadenosine moiety derived from ATP. Only two of the three sites are occupied by AdoCbl molecules, and binding of the substrate ATP to the empty site is used to eject one AdoCbl in the fashion of a rotary motor. A second nucleotide-driven step is regulated by the G protein chaperone MeaB, which mediates a tripartite exchange between ATR and MCM; the binding energy of GTP is used to select in favor of the active AdoCbl versus cobalamin itself, and the hydrolysis energy of GTP is used to promote the release of inactive cofactor from MCM, which can occur during MCM turnover. Finally, a human mutation in MCM that has no effect on enzyme activity per se was shown to block the editing capacity of MeaB, providing a mechanistic explanation for methylmalonic aciduria in this patient. — GJC

Biochemistry **48**, 5350 (2009); *Proc. Natl. Acad. Sci. U.S.A.* 10.1073/pnas.0908106106 (2009).

CREDIT: BUREK AND GREER, *NANO LETT.* 10.1021/NL902872W (2009)

MATERIALS SCIENCE

Plated Pillars

Mechanical testing of submicrometer-sized metal pillars has shown significant strengthening on decreasing the pillar dimensions. Analysis of such experiments is complicated, however, because the traditional focused ion beam method for making the pillars causes damage through the implantation of Ga^+ ions and leads to vertical tapering. Burek and Greer turned to lithographic techniques, using an electron beam to pattern a poly(methylmethacrylate) (PMMA) film. The patterned film was in turn used to template pillar growth by deposition of gold or copper through electroplating. The plating conditions could be tuned to vary the microstructure of the pillars, which ranged from single crystals to twin domain and highly nanocrystalline structures. Pillars for compressive testing were fabricated by halting plating before reaching the top of the PMMA layer; for tensile testing, the pillars were overplated with a cap to facilitate gripping of the sample. The pillars showed little tapering and exhibited diameters as small as 25 nm, much smaller than the lower limit attainable by a focused ion beam. — MSL

Nano Lett. 10.1021/nl902872w (2009).

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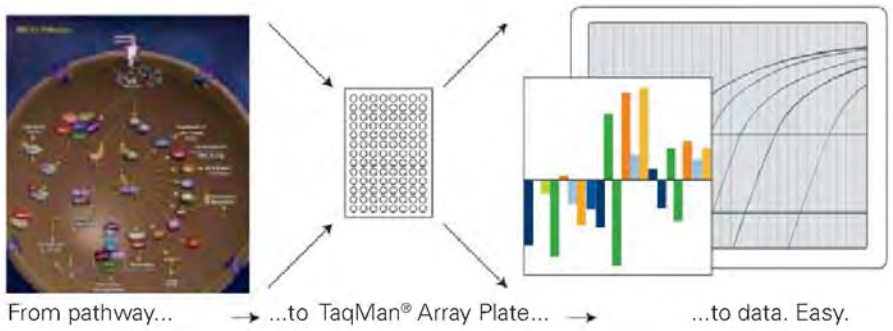

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KALTXÌ. NGARU LU FPOM SRAK?*

He never became the astronomer he dreamed of being as a child, but Paul Frommer, a linguist at the University of Southern California in Los Angeles, still got to work on other planets: He's the creator of Na'vi, the language spoken by the indigo aliens in James Cameron's *Avatar*. Na'vi is being hailed as the new Klingon, even before the film's 18 December release.

The language's phonology—its overall sound—was inspired by Cameron, who had already developed a 30-word vocabulary. Frommer modified it by adding and excluding specific sounds and sound combinations to make Na'vi seem both self-consistent and unfamiliar. "For example, English has the sounds 'f' and 'ng,' but it has no 'fng,' " Frommer says. "Na'vi does." He then added rules that specify how sounds are affected by their position in a word or phrase. The next step was morphology: word-building. The Na'vi roots for "much/great" and "understand," for example, are combined to mean "wise." Finally, Frommer developed a syntax of phrases and sentences.

One of the toughest challenges was to make sure Na'vi sounded alien to non–English speakers. "Every sound in Na'vi is found in some human language," he says, but the particular combinations are, "to the best of my knowledge, unique." Na'vi lacks a word for "science." "They would probably express the idea as 'the study of the physical world,' *tìftia kifkeyä,*" Frommer explains.

*Greetings. Are you well?

Creationism at Italian Science Agency

Italy's premier science funding agency, the National Research Council (CNR), is getting unwelcome attention for helping to fund and promote a creationist book compiled by the agency's vice president.

Evolutionism: the decline of an hypothesis was assembled by Roberto de Mattei, a historian of Christianity at the European University of Rome, from proceedings of a February meeting he organized at CNR, at which several scientists and philosophers explained why evolution is unscientific. The book, published last month, includes claims that conventional dating methods are wrong, that fossil strata resulted from the Deluge, and that dinosaurs died 40,000 years ago.

The book states that CNR contributed money for its publication (€9000, according to the newspaper *La Repubblica*). CNR President Luciano Maiani has acknowledged that CNR contributed to expenses but said the agency has not endorsed the book. In an e-mail to *Science*, however, he said, "I'd like to stress the fact that intellectual research is an open enterprise as well as my [opposition to] any form of censorship."

"Here we are not talking about the freedom of expression," counters Ferdinando Boero, a zoologist at the University of Salento in Lecce, Italy. "If you send a scientific paper stating that the Earth is flat, no scientific journal will ever publish it." Physicist Nicola Cabibbo, president of the Vatican's Pontifical Academy of Sciences, calls it ironic that "while the Church has devoted many conferences to the topic [of evolution] this year, the vice president of CNR organized conferences in favor of creationism."

Science for the Fair Sex

The New York Academy of Sciences is hosting a "Girls Night Out" series that will feature women scientists speaking on topics "close to women (and the people who love them)." The kickoff talk next month will be by anthropologist Helen Fisher on "Lust, Romance and Attachment." Next comes a talk on nutrition and diet, followed by one on "our intimate connections to trees." And finally "Survival of the Prettiest: Evolution, Beauty, and Human Happiness."

Guess girls are interested in science only if you can find a link to food, love, or makeup.

Macro Microorganisms

Nature has a richer imagination than most sculptors, as this new park in China attests. The Foraminifera Sculpture Park in Guangzhou Province officially opened this month and is dedicated to large sculptures of these single-cell marine organisms. Marine geologist Bilal Haq of the National Science Foundation got the idea of a sculpture park a decade ago after seeing palm-sized models of foraminifera in the lab of marine biologist Zheng Shouyi at the Institute of Oceanology in Qingdao, China. Zheng persuaded local authorities to pursue the idea. The 114 sculptures were carved out of marble, granite, and sandstone.

CREDITS (TOP TO BOTTOM): WETA; PAUL FROMMER; BILAL HAQ

BREAKTHROUGH OF THE YEAR

Ardipithecus ramidus

A rare skeleton draws back the curtain of time to reveal the surprising body plan and ecology of our earliest ancestors

By hand or by foot? Ardi's foot (*right*) has an opposable toe for grasping branches.

ONLY A HANDFUL OF INDIVIDUAL FOSSILS HAVE become known as central characters in the story of human evolution. They include the first ancient human skeleton ever found, a Neandertal from Germany's Neander Valley; the Taung child from South Africa, which in 1924 showed for the first time that human ancestors lived in Africa; and the famous Lucy, whose partial skeleton further revealed a key stage in our evolution. In 2009, this small cast got a new member: Ardi, now the oldest known skeleton of a putative human ancestor, found in the Afar Depression of Ethiopia with parts of at least 35 other individuals of her species.

Ever since Lucy was discovered in 1974, researchers wondered what her own ancestors looked like and where and how they might have lived. Lucy was a primitive hominin, with a brain roughly the size of a chimpanzee's, but at 3.2 million years old, she already walked upright like we do. Even the earliest members of her species, *Australopithecus afarensis*, lived millions of years after the last common ancestor we shared with chimpanzees. The first act of the human story was still missing.

Now comes Ardi, a 4.4-million-year-old female who shines bright new light on an obscure time in our past. Her discoverers named her species *Ardipithecus ramidus*, from the Afar words for "root" and "ground," to describe a ground-living ape near the root of the human family tree. Although some hominins are even older, Ardi is by far the most complete specimen of such antiquity. The 125 pieces of her skeleton include most of the skull and teeth, as well as the pelvis, hands, arms, legs, and feet. (The 47-million-year-old fossil of the early primate called Ida is also remarkably complete, but she is not a direct ancestor to humans, as initially claimed during her debut this year.)

When the first fossils of Ardi's species were found in 1994, they were immediately recognized as the most important since Lucy. But the excitement was quickly tempered by Ardi's poor condition: The larger bones were crushed and brittle, and it took a multidisciplinary team 15 years to excavate Ardi, digitally remove distortions, and analyze her bones.

Ardi's long-awaited skeleton was finally unveiled in 11 papers in print and online in October (*Science*, 2 October, pp. 60–106). Her discoverers proposed that she was a new kind of hominin, the family that includes humans and our ancestors but not the ancestors of other living apes. They say that Ardi's unusual anatomy was unlike that of living apes or later hominins, such as Lucy. Instead, Ardi reveals the ancient anatomical changes that laid the foundation for upright walking.

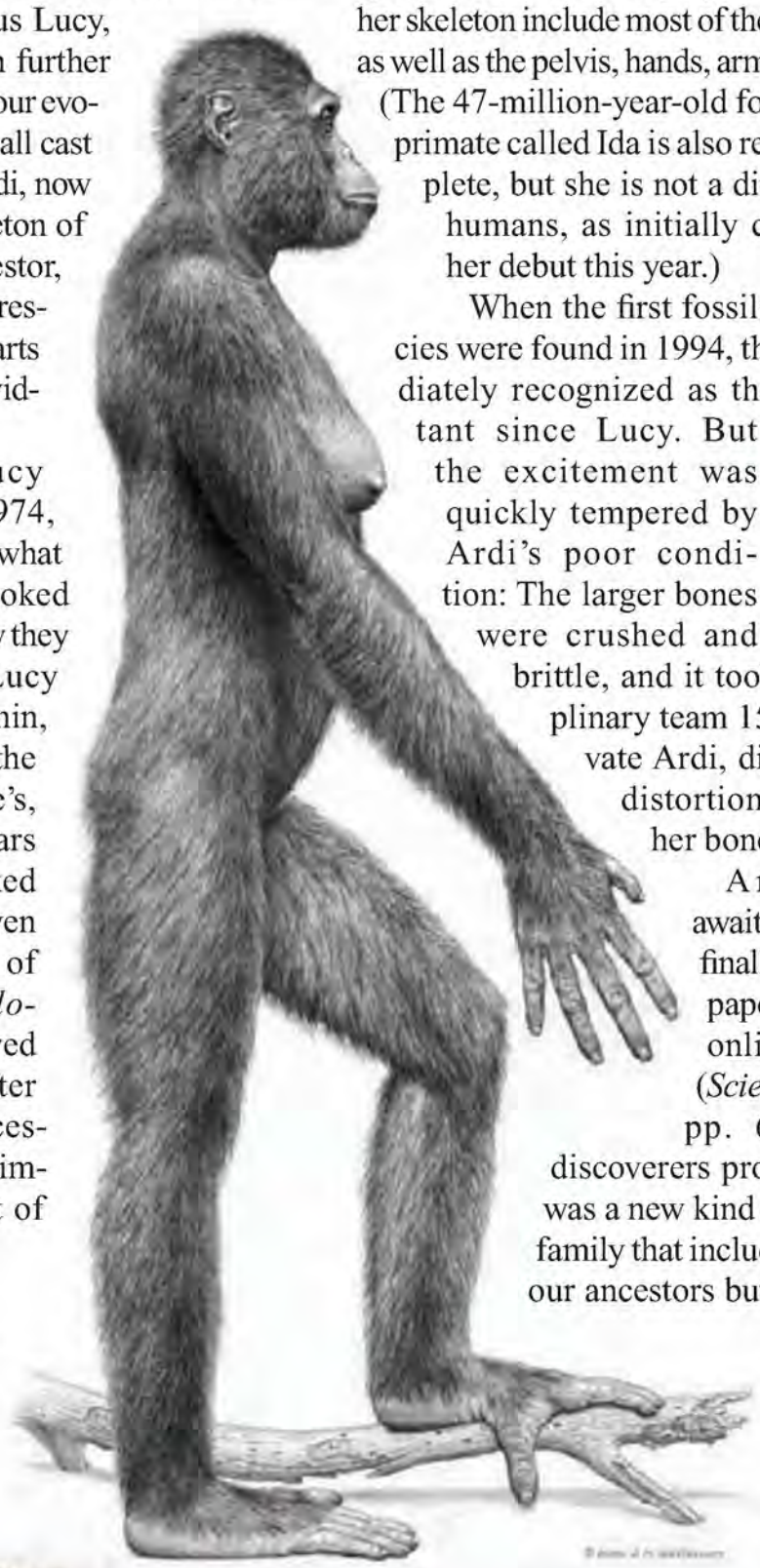
Not all paleoanthropologists are convinced that *Ar. ramidus* was our ancestor or even a hominin. But no one disputes the importance of the new evidence. Only a half-dozen partial skeletons of hominins older than 1 million years have ever been published. And having a skeleton rather than bits and pieces from different individuals not only provides a good look at the whole animal but also serves as a Rosetta stone to help decipher more fragmentary fossils. As the expected debate over Ardi's anatomy and relations to other primates begins, researchers agree that she and the other specimens of her species provide a wealth of new and surprising data on some of the most fundamental questions of human evolution: How can we identify the earliest members of the human family? How did upright walking evolve? What did our last common ancestor with chimpanzees look like? From now on, researchers asking those questions will refer to Ardi.

BREAKTHROUGH **ONLINE**

For an expanded version of this section, with references, links, and multimedia, see www.sciencemag.org/btoy2009 and sciencecareers.org.

Body of evidence

Ardi's biggest surprise is that she was not transitional between *Australopithecus* and a common ancestor that looked like living chimpanzees and gorillas. Standing 120 centimeters tall, Ardi had a body and brain only slightly larger than a chimpanzee's, and she was far more



Ancient upstart. Ardi may have moved upright on branches and on the ground, a key step in the evolution of upright walking.

CREDITS (TOP TO BOTTOM): © 2005, JAY MATTERNES; © 2008 JAY MATTERNES; (BACKGROUND) D. BRILL

primitive than Lucy. But she did not look like an African ape, or even much like the known fragments of more ancient apes.

When researchers studied her face and teeth, they found derived features that tie *Ardipithecus* to all later hominins, including Lucy's species and us. For example, Ardi's muzzle juts out less than a chimpanzee's does. Even males of her species lacked the large, sharp, daggerlike upper canines seen in chimpanzees. The base of her skull is short from front to back, as in upright walkers, rather than elongated, as in quadrupedal apes.

In addition, Ardi's pelvis convinced her discoverers that she did indeed walk upright—long the defining trait for being a member of the human family. The upper blades of Ardi's pelvis are shorter and broader than in living apes, lowering her center of gravity so she could balance on one leg at a time while walking, for example. But she didn't walk as well as humans or Lucy. Her pelvis was useful for both climbing and upright walking, making her a "facultative" biped, according to her discoverers.

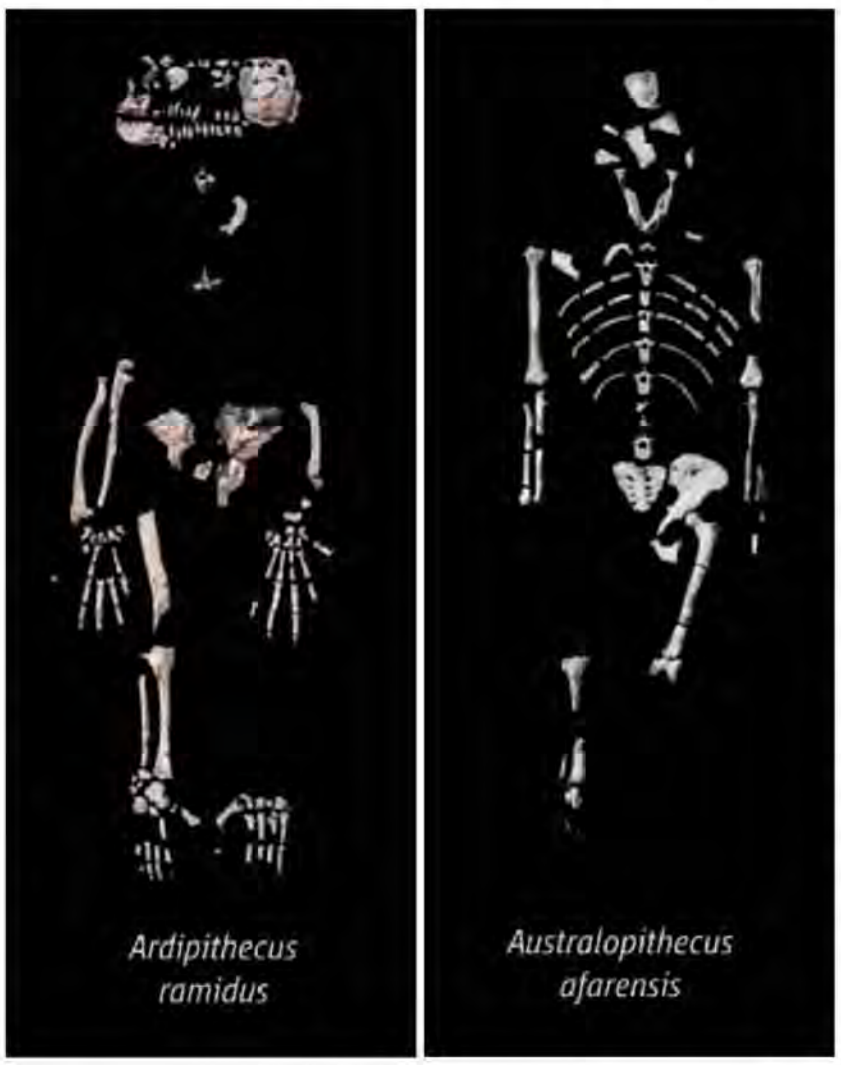
Ardi's remarkably complete hand and foot bones add to this picture. Her wrist joints were not as stiff as those of African apes, and the bones of her palm were short, indicating that she did not knuckle-walk like chimpanzees or swing beneath tree branches, the discoverers say. Yet Ardi's foot was more rigid than a chimpanzee's, suggesting that it was an odd mosaic used for both upright walking on the ground and careful climbing and walking atop branches in the trees. Indeed, Ardi's long curving fingers and opposable big toe suggest she grasped tree branches.

If so, our ancestors began walking upright while still living primarily in a woodland rather than in more open, grassy terrain, as once believed. The international discovery team went to great lengths to reconstruct the scene where Ardi took her first steps, collecting 150,000 specimens of fossil plants and animals from Aramis and nearby. After using radiometric methods to tightly date the fossil-bearing sediments to 4.4 million years ago, the team concluded that Ardi lived on an ancient floodplain covered in sylvan woodlands, climbing among hackberry, fig, and palm trees, and coexisting with monkeys, kudu antelopes, and peafowl.

Human relations

At face value, Ardi is a hominin—if you define hominin on the basis of traits in the face, skull, and teeth. Many researchers who have read the descriptions of *Ardipithecus* or seen casts of the fossils agree on this. But since Lucy's discovery, the gold standard for identifying a hominin has been walking upright. Among primates, only humans and our closest relatives were habitual bipeds. On this point, Ardi stands on shakier ground.

The pelvis, which provides the pivotal evidence for upright walking, is fragmentary and crushed—parts of it have been called "Irish stew"—and outside researchers want to review its reconstruction. The discoverers note, however, that the interpretation of upright walking rests on traits in the foot and on the best-preserved portions of the original pelvis, not the reconstruction.



Lucy, meet Ardi. Ardi (*left*) this year joined Lucy as one of the rare fossil hominin skeletons that shape our understanding of human evolution.

A few outside researchers who have already seen the cast of the pelvis agree that it shares some key traits with later hominins, such as the shape and size of a large opening known as the sciatic notch. Yet Ardi's hands and feet are so primitive that some researchers strongly question whether she really walked upright more often than other apes or was less able to climb and swing beneath branches. The next steps will be to further compare Ardi's bones with those of more ancient apes and to see how her unique anatomical features affected how she moved.

Many researchers also challenge the papers' forceful argument that Ardi reveals the basic body plan of the common ancestor of humans and chimpanzees. They point out that Ardi lived perhaps 1 million to 3 million years after that ancestor—plenty of time for evolutionary change. Some also question the social implications of *Ardipithecus* males' reduced canines, which the discovery team interprets as implying less male-male aggression than is seen in chimps.

The debate reveals how hard it is to identify upright walking in such an early hominin. Must Ardi walk upright like an australopithecine to be admitted to the human family? Or is it enough that she walked upright in an intermediate manner, if her face, skull, and canines align her with later protohumans? Ardi is already prompting some to ask whether habitual upright walking is essential to being a hominin. Perhaps some ancient apes became hominins head first.

There's precedent for new hominin fossils provoking controversy and redefining what it means to be a member of the human family. Many thought a big brain and tool use emerged in concert with upright walking—until Lucy, with her chimp-sized brain, proved that upright walking came first.

As researchers ponder the definition of a hominin, they also wonder exactly where Ardi fits in our family tree. The discovery team suggested as one hypothesis that *Ardipithecus* gave rise to Lucy's genus *Australopithecus*, which is generally thought to have led to our own genus, *Homo*. But they also noted that Ardi could have been a side branch, an extinct lineage that was a sister species to our direct ancestors. As the study of Ardi widens to include new collaborators, the team is granting requests to view the casts and will return to Aramis to search for more fossils.

In the year of the bicentennial of Darwin's birth, it seems fitting that researchers finally broke through the 4-million-year barrier to understanding our origins. Models for our earliest ancestors can now be informed by plenty of fresh data and at least one body of hard evidence. **–ANN GIBBONS**

CREDITS: TIM WHITE; (BACKGROUND) D. BRILL

THE RUNNERS-UP >>

Opening Up the Gamma Ray Sky

LIKE A LIGHTHOUSE BLINKING IN THE NIGHT, A pulsar appears to flash periodically as it spins in space, sweeping a double cone of electromagnetic radiation across the sky. Since the discovery of the first pulsar 4 decades ago, astronomers have detected hundreds more of these enigmatic objects from the pulsing radio waves they emit. Now, astronomers have opened a new channel of discovery—the highly energetic gamma ray spectrum—to find pulsars that radio observations could not detect. The advance, part of a torrent of recent gamma ray observations, is giving researchers an improved understanding of how pulsars work, along with a rich haul of new pulsars that could help in the quest to detect gravitational waves.

The findings come from the Fermi Gamma-ray Space Telescope, which has been mapping the gamma ray universe since it was launched by NASA in June 2008. Combing through data the telescope collected in its first few months, an international team discovered 16 new pulsars; strong gamma ray pulsations from eight previously known pulsars with spin times of milliseconds, proving that these objects pulse brightly at gamma wavelengths as well as in the radio range; and high-energy gamma rays from the globular cluster 47 Tucanae indicating that the cluster harbors up to 60 millisecond pulsars.

Those Fermi results might be just the beginning. Armed with their new knowledge of pulsar behavior, researchers are checking whether some of the unidentified gamma ray sources Fermi has detected might be pulsars. In November alone, teams of astronomers in the United States and France discovered five new millisecond pulsars by training ground-based radio telescopes on candidate objects Fermi had pointed out—a much more targeted search technique than scanning the sky blindly with ground-based radio telescopes.

Gamma ray beams of pulsars are believed to be wider than their radio beams, so in principle a space-based gamma ray telescope should be more likely to encounter and discern a pulsar's sweep than a radio telescope on Earth is. However, Fermi's forerunner—the Compton Gamma Ray Observatory, which flew from 1991 to 2000—did not have much luck finding these objects. What has made the difference is Fermi's high sensitivity, which enables it to detect pulsations that would have been too faint for Compton.

Already, the discoveries are shedding new light on the physics of pulsars. Researchers

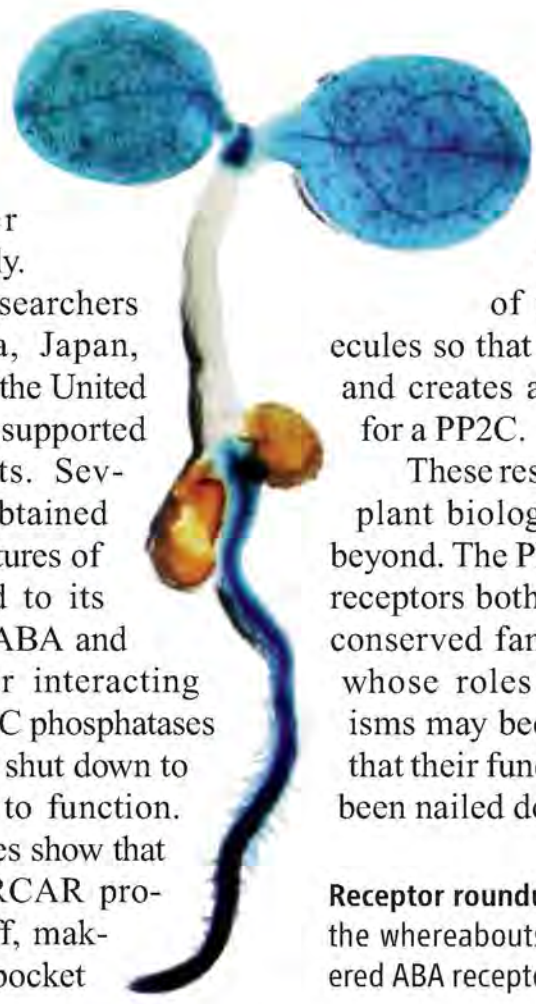
ABA Receptors

ALTHOUGH "FIGHT OR FLIGHT" is not in their behavioral repertoire, plants have their equivalent of an adrenaline rush: a chemical called abscisic acid (ABA). High concentrations of ABA keep seeds dormant and help curtail water loss and inhibit root and other vegetative growth when times are tough. The receptors for this key plant hormone have long eluded plant biologists, sending them down false trails and leaving research in disarray. But in May, two independent teams, taking different approaches, identified the same family of proteins as the receptors. By late fall, several other groups had confirmed the connection between ABA and the PYR/PYL/RCAR proteins. As one leader in the field put it: "The ABA receptor field finally has a success."

One team, based in Germany, homed in on these receptors by looking for proteins that bind to enzymes called ABI1 and ABI2, known to help spur ABA activity. They found two, calling each a "regulatory component of ABA receptor" (RCAR). A second team, based in California, tracked down an ABA receptor by figuring out what pyrabactin, which revs up ABA activity, interacts with. This group called the receptor PYR1. Both teams discovered that their receptors were part of the same 14-member protein family.

Other researchers from China, Japan, Europe, and the United States have supported these results. Several have obtained crystal structures of ABA bound to its receptor or ABA and the receptor interacting with the PP2C phosphatases that must be shut down to allow ABA to function. The structures show that PYR/PYL/RCAR proteins pair off, making a gated pocket that ABA nestles into. ABA changes the shape of the pair of molecules so that the "gate" closes and creates a binding surface for a PP2C.

These results are a boon for plant biology—and possibly beyond. The PP2C and the ABA receptors both belong to highly conserved families of proteins whose roles in other organisms may become clearer now that their function in plants has been nailed down.



Receptor roundup. Blue stain shows the whereabouts of a newly discovered ABA receptor in a seedling.

CREDITS (TOP TO BOTTOM): NASA E/PO, SONOMA STATE UNIVERSITY, AURORE SIMONNET; YUE MA *ET AL.*, *SCIENCE*

Flash. Pulsar CTA 1 is one of many discoveries by the Fermi Gamma-ray Space Telescope.

know that pulsars are fast-spinning neutron stars with powerful magnetic fields that accelerate particles to near–light speed and shoot them out from the poles. Those hot jets of matter give off gamma rays. But how are the magnetic fields structured, and exactly where do the particle beams emanate from? In one type of model, the jets erupt from the polar caps on the surface of the neutron star; in another, the beam originates above the poles, thousands of kilometers out in space.

An analysis of the gamma ray emission from the pulsars Fermi observed dealt a severe blow to the polar cap model, astrophysicists say. Instead, the observations suggest that the bulk of the emission comes from a location in the outer magnetosphere. Such detailed examination of how pulsars work would be impossible through radio observations alone, because radio waves make up only a minute fraction of the pulsar's total energy; gamma rays represent a much more substantial chunk of its radiation.

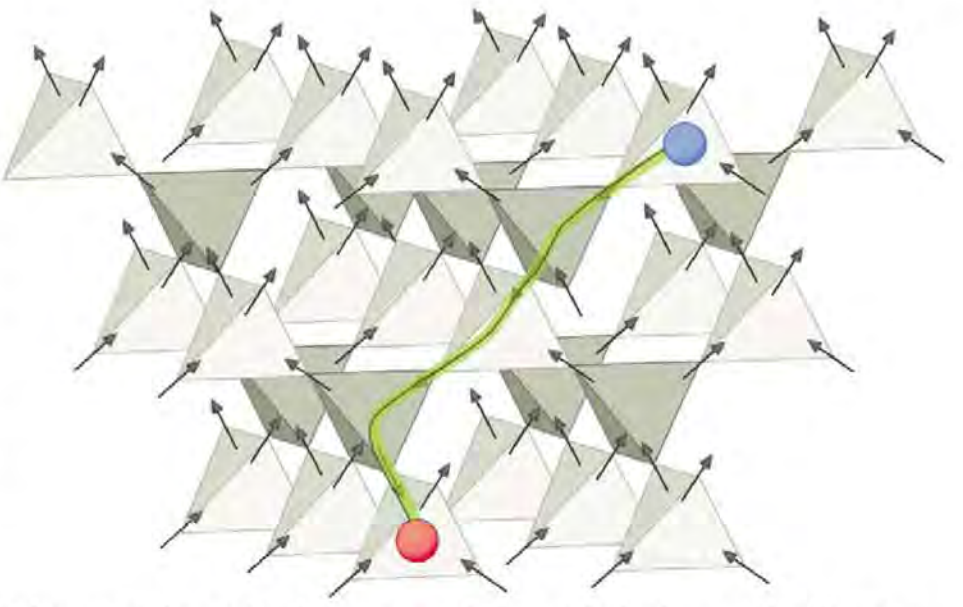
Astrophysicists say the pulsar results herald further discoveries about many other types of cosmic objects. The more than 1300 gamma-ray sources Fermi has detected include starbursting galaxies, gamma ray bursts, and the black holes at the center of galaxies. In November, teams at two ground-based gamma ray telescopes, in combination with Fermi, solved a long-standing mystery by tracing cosmic rays, highly energetic particles from space, to their birthplaces inside exploding stars (*Science*, 20 November, p. 1047). The new pulsars themselves could help researchers detect gravitational waves—ripples in the fabric of spacetime, which should cause apparent changes in the rotation rate of the most rapidly spinning pulsars.

Mock Monopoles Spotted

IN DR. SEUSS'S FAMOUS CHILDREN'S BOOK *HOW THE GRINCH STOLE Christmas*, the curmudgeonly protagonist snaps, "If I can't find a reindeer, I'll make one instead!" Physicists have taken a similar approach to the pursuit of a long-sought particle called a magnetic monopole. They still haven't found such a creature, but this year two teams created ripples, or "quasiparticles," inside magnetic crystals that act like monopoles.

As far as physicists know, every magnet has a north pole and a south pole. However, theorists have speculated about fundamental particles that have only one or the other. In 1931, the British theorist Paul Dirac argued that the existence of such monopoles would explain the quantization of electric charge. Monopoles are also predicted by "grand unified theories" that treat the electromagnetic, the weak, and the strong forces as different aspects of one thing.

The monopoles reported in September exist only in materials such as holmium titanate and dysprosium titanate, which are known as spin ices. Within them, the gyrating and magnetic holium or dysprosium ions sit at the corners of four-sided pyramids, or tetrahedra, just as hydrogen ions do in ice. At low temperatures, two ions in each tetrahedron point their north poles inward toward the tetrahedron's center and two point their north poles outward. Flipping one ion then creates one imbalanced tetrahedron with three ions pointing in and another tetrahedron with only one ion pointing in. Flip more spins and the imbalances can shuffle about independently, acting like monopoles.



Poles apart. In a spin glass, monopoles are tetrahedrons with either one (blue ball) or three (red ball) magnetic ions pointing inward.

Such "spin systems" provide a playground for theorists and experimentalists alike. The observed monopoles illustrate the richness of such systems in a simple way.

CREDITS (TOP TO BOTTOM): NASA E/PO, SONOMA STATE UNIVERSITY, AURORE SIMONNET; P. HUEY/*SCIENCE*

SCORECARD

Rating Last Year's Areas to Watch

(For this year's predictions, see page 1606.)

Plant genomics

The genome sequences of cucumber, sorghum, and two strains of maize saw print in 2009, a cause for celebration. Cassava and oil palm were sequenced as well, and there has been progress on numerous other plants, although perhaps not as much as *Science* forecast.

Ocean fizz

The inevitable acidification of the ocean by rising atmospheric carbon dioxide garnered more public attention in 2009, but—as anticipated—not much. The expected bad news about generally harmful effects on living things kept coming, and hot spots of particularly rapid acidification turned up, but nothing pushed world attention across a threshold. Climate negotiations in Copenhagen got no boost from outcries over the one sure greenhouse impact.

Neuroscience in court

In March, defense attorneys in a child custody case in southern California submitted as evidence—but later withdrew—fMRI scans purportedly showing that their client was telling the truth. In November, defense attorneys for a convicted murderer in Illinois used fMRI scans to argue that their client should be spared the death penalty because of a brain disorder. After much deliberation, the jury decided otherwise. Interest in using neuroimaging in court cases continues to grow, but 2009 wasn't the watershed year we predicted.

Road to Copenhagen

A new American president pledging to pass greenhouse gas restrictions, growing international momentum, and increasingly clear climate science might well have paved the way for a historic global agreement on emissions at the U.N. conference in Denmark. But the U.S. Senate and international negotiators couldn't get their act together before the meeting, which ended after this issue went to press. Emissions limits will get other chances in 2010, but the looming U.S. congressional elections and the continuing partisanship in Washington remain major obstacles to any global agreement.

Darkness visible

As predicted, dark matter remained murky. Two years ago, the ATIC balloon experiment reported an excess of electrons and positrons from space at a particular energy, which might be a sign of dark matter particles annihilating each other. This year, the orbiting Fermi Gamma-ray Space Telescope saw no such excess. The Fermi spectrum wasn't exactly what astrophysicists expected, however, and data from the orbiting PAMELA particle detector still show an increase in the ratio of positrons to electrons. These could be signs of dark matter, but the case is hardly clear.

Defining species

Darwin would have been pleased with progress in the genetics of speciation in the year of his 200th birthday celebration. The number of speciation genes has jumped from five in 2006 to about 15, depending on how a speciation gene is defined, with discoveries in mammals and yeast as well as the usual fruit flies. Researchers also succeeded in pinning down other DNA, including several regulatory regions involved in helping to define new species, and worked on understanding genomewide influences on speciation.

Tevatron's triumph

It didn't find the Higgs boson as we all but predicted it would, but the aging atom smasher at Fermi National Accelerator Laboratory (Fermilab) in Batavia, Illinois, scored a victory of sorts. The U.S. Department of Energy announced that it plans to run the Tevatron through 2011, which should allow physicists at Fermilab either to spot signs of the most-coveted particle or to rule out its existence in the most likely range of masses. Physicists at the European particle physics laboratory, CERN, near Geneva, Switzerland, are finally starting up the more-powerful Large Hadron Collider, so the race for the Higgs will likely come down to the wire in 2012.

Live Long and Prosper

IT'S NOT PONCE DE LEÓN'S VISION of the fountain of youth: the secretion of a dirt-dwelling bacterium from Easter Island. But this year researchers showed that the compound, called rapamycin, boosts longevity in mice, the first time any drug has stretched a mammal's life span.

Doctors prescribe rapamycin to battle kidney cancer and to stymie rejection of transplanted organs. After the U.S. National Institute on Aging added the drug to its list of molecules that might increase rodent life span, the three U.S. labs that test such candidates

Methuselah mice. Longevity soared as much as 14% in rodents fed the drug rapamycin.

CREDITS (TOP TO BOTTOM): (ICONS) Y. GREENMAN/*SCIENCE*; JUPITERIMAGES

started feeding rapamycin to mice when they were 600 days old, comparable to 60-year-old people. The rapamycin-rich diet added between 9% and 14% to the rodents' life span. Researchers had achieved similar feats in worms and flies, but the result was a first in mammals—and especially encouraging because the animals were already past their prime.

The drug's mechanism has scientists puzzled. Rapamycin curbs the TOR biochemical pathway, which is involved in everything from protein synthesis to cell division. However, the drug didn't thwart any specific cause of death: The mice suffered the full range of old-age infirmities such as ulcers and heart failure. And because the mice didn't become skinny, the researchers doubt that rapamycin works similarly to calorie restriction (CR)—an extreme diet that can increase longevity in mice and some other lab organisms—although other scientists think there might be a connection.

Meanwhile, another study released this year brought us closer to answering the big question about CR: whether it's effective in humans. The first primate trials, on rhesus monkeys, started 20 years ago. Now the animals are starting to die from age-related causes, and the early results indicate that they are outlasting their well-fed contemporaries.

Rapamycin undermines the immune system, and only zealots can stick to CR. So neither is likely to be a practical life extender. But they might lead researchers to more palatable alternatives for slowing aging or at least increasing how long we remain healthy.

CREDITS (TOP TO BOTTOM): NASA AMES/NORTHROP GRUMMAN; JUPITERIMAGES

Watch out! The LCROSS spacecraft (*foreground*) glimpsed water thrown up when the spent rocket (*background*) hit the moon.

An Icy Moon Revealed

PLANETARY SCIENTISTS FINALLY PROVED THIS YEAR that a barren, often boiling-hot body like the moon can harbor water ice. The finding renewed prospects for reading an eons-long environmental record and for literally fueling the exploration of the solar system.

An icy moon hadn't been a totally outrageous idea. Radar probing of Mercury from Earth in the early 1990s had revealed what seemed to be water ice buried beneath the floors of impact craters on Mercury. The deposits appeared only in polar craters whose rims cast permanent shadows across their floors, ensuring the required perpetual cold. Perhaps, scientists reasoned, over the eons a bit of the water from impacting comets and icy asteroids got frozen into the permanently shadowed craters. Orbiting radar eventually hinted at ice in polar lunar craters, too, but that notion remained controversial, even after an orbiting instrument in 1998 detected high polar concentrations of hydrogen that could be part of buried water molecules.

In the end, it took slamming a 2-ton spent rocket stage into a permanently dark, frigid crater called Cabeus at 7200 kilometers per hour to coax a few liters of water into sight. The $80-million Lunar Crater Observation and Sensing Satellite (LCROSS) mission returned clear spectroscopic signatures of water vapor, ice, and water-derived hydroxyl in the impact plume.

LCROSS also returned evidence for a source of the moon's water. Its sensors detected molecules such as carbon monoxide, methane, and methanol that had been buried with the water ice. Those are just the sort of compounds found in comets and icy asteroids, so at least a few spots on the moon may have retained a trace of the bodies that have been bombarding the moon for eons.

Icy stores of lunar water might hold records of lunar impacts over billions of years. Astronauts might drink the water, grow food with it, or even split its molecules into hydrogen and oxygen for rocket fuel. One problem: Someone would have to figure out how to conduct coring and mining operations on the moon at just 40° above absolute zero.

BREAKDOWN REVISITED

TRYING TO STAY AFLOAT

WHEN LAST YEAR'S FINANCIAL crisis (*Science*'s "Breakdown of the Year" for 2008) swept the globe, doomsayers predicted a calamity for research. They were partly right: 2009 has been a tough year for many U.S. academic institutions dependent on state funding or endowments. But it has also been a banner year for thousands of individual scientists, whose labs have benefited from billions of dollars in U.S. government stimulus funding (*Science*, 27 November, p. 1176). And in much of the rest of the world, research institutions so far seem to be weathering the storm.

California, the most populous state, is in especially dire shape. "Win a Nobel, get a pay cut," Elizabeth Blackburn quipped to reporters after learning that she had won the 2009 medicine prize for her work on telomeres. Blackburn, an Australian-born biochemist at the University of California (UC), San Francisco, suffered a 4% salary cut this summer (in the form of an 11-day furlough). She and thousands of other faculty members in the 10-university UC system were taxed to help erase an $813 million deficit caused by a continued drop in support from a state fighting to stave off bankruptcy. Anticipating an even larger state deficit next year, UC regents last month increased tuition fees for next year by 32%, to $10,300, further eroding what was once one of the country's best bargains in higher education.

California is not alone in its misery. A survey last month of the 188-member Association of Public and Land-grant Universities (APLU) found that 87% of respondents had suffered cuts in state funding, an important source of revenue for many public universities, with the decreases averaging 11.4%. Those hardest hit have eliminated departments and laid off tenured professors. Private universities—including Harvard, Stanford, and Yale, some of the world's wealthiest—have reduced staff and services and halted long-planned construction (*Science*, 27 February, p. 1157) after their endowments shrank by 20% to 27%. But so far, they have avoided faculty layoffs.

"Those publics that have historically had high state support and relatively low tuition, like California, have been hurt the most by a decline in state support," says Robert Berdahl, president of the 62-member Association of American Universities and former chancellor of the system's flagship institution, UC Berkeley. "And those privates that have been most dependent on endowments have also been hurt badly."

At the same time, some institutions are managing to stay afloat—or even thrive. The University of Michigan has kept its $5.4 billion annual budget in balance despite a drop in state funding by judicious trimming—planting fewer bulbs and trees at the Ann Arbor campus, for example—and by finding additional sources of revenue. Another flagship state university, the University of Texas (UT), Austin, has avoided cuts to its educational programs

Gene Therapy Returns

GENE THERAPY—REPAIRING MALFUNCTIONING cells by mending their DNA—offers an elegant solution to diseases caused by a single flawed gene. Since the first human study began in 1990, however, the field has struggled with technical challenges and setbacks such as the death of a volunteer in a trial. But this year, gene therapy turned a corner, as researchers reported success in treating several devastating diseases:

• **Leber's congenital amaurosis (LCA)**, a rare form of inherited blindness that strikes in infancy. Researchers in the United States and the United Kingdom injected one eye of LCA patients with a harmless virus carrying a gene coding for an enzyme needed to make a light-sensing pigment. In the first completed trial, the light sensitivity of all 12 partially blind patients improved. Four children gained enough vision to play sports and stop using learning aids at school. (Another team using a similar approach gave full color vision to squirrel monkeys born with red-green colorblindness.)

• **X-linked adrenoleukodystrophy (ADL)**, a brain disorder that usually kills boys before they're teenagers. The disease involves a flaw in a gene that makes a protein that helps maintain the myelin sheath around nerves. A French team inserted a corrective gene into the blood cells of two 7-year-old boys with ADL, and some of the cells began making the missing protein and apparently migrated into their brains. Two years later, the progressive brain damage typical of ADL has stopped. The trial is also the first to carry the gene into cells with a disabled HIV virus, which should be less likely than older vectors to cause cancer.

Success. Blind patients regained some vision after treatment to repair an enzyme-making gene.

CREDIT: STEPHENVOSS.COM

• **"Bubble boy" disease**: severe combined immunodeficiency (SCID) due to a lack of an enzyme called adenosine deaminase. In January, Italian researchers gave an update on an 8-year-old trial for children with the disease. Eight of 10 patients no longer need enzyme-replacement therapy and are living normal lives. None suffered serious side effects from the therapy. (Gene therapy for a related disease, X-linked SCID, restored the immune systems of 19 infants but caused leukemia in five of them, one of whom died.)

Clinical results for other genetic diseases are expected out soon, and more trials using the new, safer vectors are gearing up.

and become a buyer of prime research talent. "The department is growing, and we're part of a cohort of new people; … it's a fabulous feeling," William Hanks told *The New York Times* last month, explaining why he and his wife, Jennifer Johnson-Hanks, both cultural anthropologists, had decided to leave UC Berkeley for UT Austin.

Research universities in Europe and Asia have reported fewer direct impacts from the recession, as many top private institutions there depend far less on endowments than their U.S. counterparts do and are less prone to financial shocks. But changes may be coming. This summer, a new government in Japan froze a planned multibillion-dollar growth in research spending and seems poised to slash support for science as part of its plan to shrink recession-triggered budget deficits (*Science*, 20 November, p. 1046). In Europe, Portugal and Italy have already experienced university funding reductions of 10% to 20%. Ireland faces possible cuts of 6% to 10% in university funding in the next 2 years, according to the European University Association, which also notes that eastern European universities are under heavy pressure.

So what's in store for 2010? A majority of respondents to the APLU survey are bracing for another round of state cuts. "Many people think that the state funding will never quite recover, especially in places that have been hurt the worst," says Berdahl. And facing growing political opposition to more tuition hikes, university administrators aren't sure how best to buffer themselves against the continuing economic storms.

–JEFFREY MERVIS AND ELIOT MARSHALL

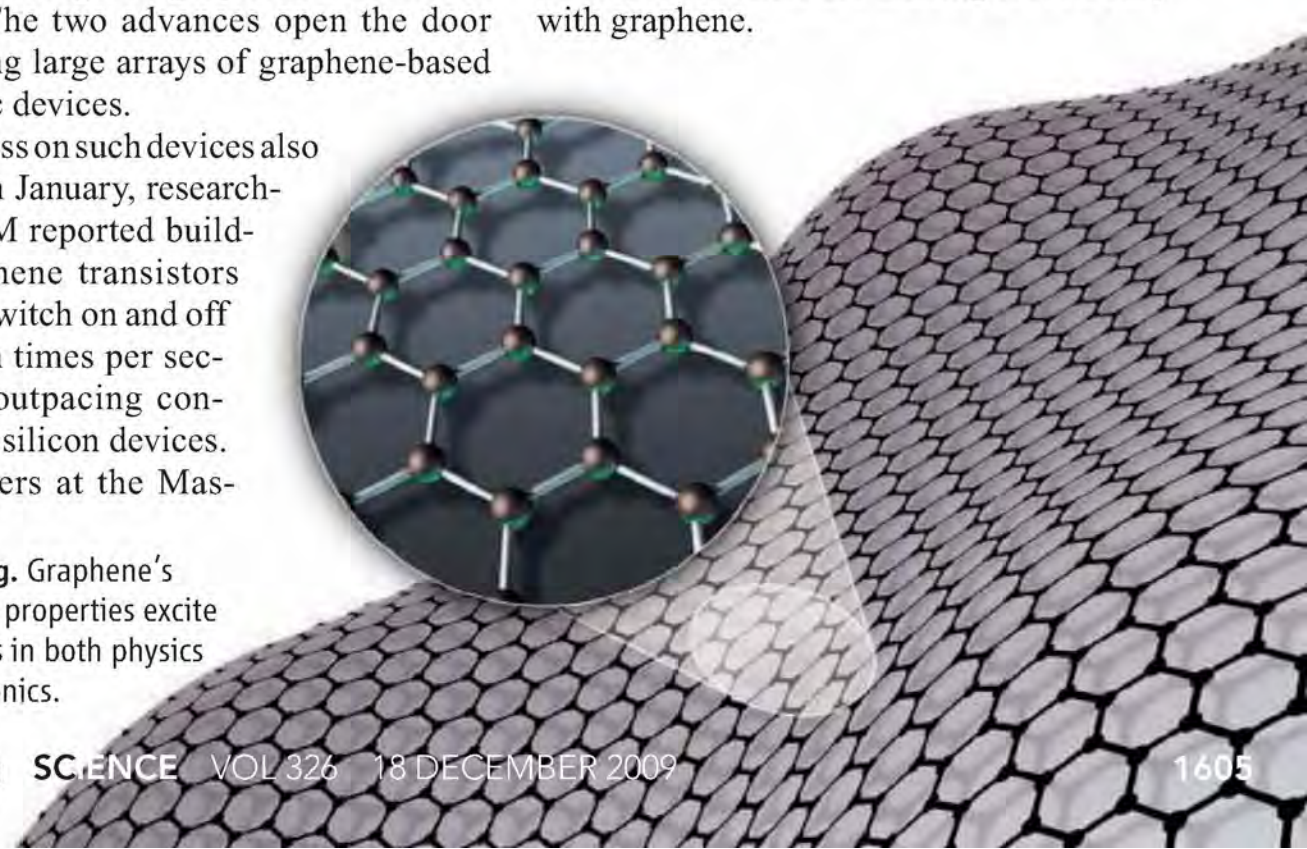
Graphene Takes Off

PROGRESS IN MATERIALS SCIENCE OFTEN plods. Graphene soars. Since 2004, when researchers in the United Kingdom discovered a simple way to peel the single-atom-thick sheets of carbon atoms off chunks of graphite, researchers have scrambled to study this ultimate membrane. This year they took it to a new level, with a string of discoveries that include new fundamental insights and ways to make large graphene sheets and turn them into novel devices.

Much of graphene's fascination lies in the way it conducts electrons. Its near-perfect atomic order—a chicken wire–like lattice of carbon atoms—allows electrons to flow through it at ultrafast speeds. That property enables physicists to use it as a simple test bed for some of the unusual features of quantum mechanics. Last month, for example, separate research groups in New York and New Jersey confirmed that graphene's electrons exhibit the fractional quantum Hall effect, in which electrons act collectively as if they are particles with only a fraction of the charge of an electron. This behavior was spotted decades ago in some multilayer semiconductors but never before in such a simple material.

Simplicity reigned elsewhere as well. In May, researchers at the University of Texas, Austin, reported that they had made graphene films up to a centimeter square by growing them atop thin copper foils. A team at Cornell University modified their technique to grow graphene on silicon wafers. The two advances open the door for making large arrays of graphene-based electronic devices.

Progress on such devices also surged. In January, researchers at IBM reported building graphene transistors that can switch on and off 26 billion times per second, far outpacing conventional silicon devices. Researchers at the Massachusetts Institute of Technology chipped in with a graphene frequency multiplier for electronic signals, which could lead to new applications in communication and sensing. And elsewhere, researchers turned out everything from a graphene-based scale capable of weighing small molecules to a superfast graphene photodetector. Simple or not, researchers are making it look easy with graphene.



Electrifying. Graphene's conductive properties excite researchers in both physics and electronics.

CREDITS (TOP TO BOTTOM): M. TWOMBLY/*SCIENCE*; C. BICKEL/*SCIENCE*

Breakthrough of the Year

Hubble Reborn

Grand finale. The last Hubble repair mission gave the space telescope a new lease on life.

IT WAS AN AGING WORKHORSE THAT ALMOST GOT PUT out to pasture. But this fall, the Hubble Space Telescope began snapping the best images of its 19-year career, thanks to a successful servicing mission in May that has extended the instrument's life by another 5 years.

The mission capped a long battle within NASA to keep Hubble alive after former NASA Administrator Sean O'Keefe announced the cancellation of a planned 2004 shuttle flight to service the telescope. NASA officials pondered sending a robot to make the necessary repairs, but many experts saw that as an unrealistic proposition that would doom Hubble. Proponents of maintaining the telescope's operations heaved a sigh of relief in 2006 when O'Keefe's successor, Michael Griffin, asked the agency's astronauts to buckle up for a final journey to refurbish the instrument.

In May, a seven-member crew on board the shuttle Atlantis traveled 500 kilometers above Earth, making five spacewalks over 11 days to carry out a set of complex and risky maneuvers. By the end, they had checked off all the tasks on their list: replacing the Wide Field Camera 2 with the new Wide Field Camera 3, which offers more than 10 times the image resolution; installing the Cosmic Origins Spectrograph, which enhances Hubble's ability to take ultraviolet spectra; and making fixes to two existing devices, the Advanced Camera for Surveys and the Space Telescope Imaging Spectrograph.

On 9 September, NASA released the results of the effort: spectacular images of the Butterfly Nebula, the Omega Centauri globular cluster, and other stellar wonders. Hubble was back in business. Now, scientific work using Hubble data is picking up pace: In recent months, for example, the instrument has delivered the most detailed pictures yet of the nearby spiral galaxy, M83, which should help researchers learn more about star birth in its core.

AREAS TO WATCH

IPS CELLS. Last year's Breakthrough of the Year, the ability to reprogram adult skin cells into induced pluripotent stem (iPS) cells that can be coaxed to develop into various mature cell types, promises to usher in a new wave of research. Using these methods, researchers can create cells from individual patients and examine them for physiological and genetic abnormalities or use them to test potential therapies. Scientists have already created iPS cells from people with type 1 diabetes, Parkinson's disease, and at least a dozen other disorders. Look for the number to grow in 2010 as more researchers get in on the act and, with luck, start gaining new insights into these conditions.

COSMIC EYE. An innovative space-based particle physics experiment called the Alpha Magnetic Spectrometer (AMS) will finally be delivered to the international space station in July. Nobel physicist Samuel Ting led the international team behind AMS, which will analyze cosmic rays for evidence of antimatter, dark matter, and strangelets. Originally due for launch in 2003, it was grounded by the Columbia disaster, a situation that looked permanent. But in 2008, the U.S. Congress passed a bill mandating that NASA launch the $2 billion instrument.

At last. The Alpha Magnetic Spectrometer will lift off 7 years later than planned.

EXOME STUDIES. In 2010, scientists will sequence the protein-coding DNA of thousands of people's genomes in hopes of finding new genes underlying human diseases. Such "exome sequencing" studies are already revealing the genetic causes of mysterious hereditary illnesses. They might also fill in the gaps left by so-called whole genome association studies, which use DNA chips to scan the genome for disease risk markers. Although wildly popular in recent years, these studies have failed to explain much of the heritability of common diseases and traits. Some researchers are betting that rarer variants found through sequencing will unveil this genetic "dark matter."

BIOCHEMISTRY BEATS CANCER? Will a metabolic quirk of cancer cells first noticed in the 1920s finally pay off with new treatments? To break down glucose, tumor cells often switch from the usual oxygen-demanding pathway to an oxygen-free alternative called glycolysis. Disrupting the cells' unorthodox metabolism has already become the talk of conferences, the business plan of at least one biotech start-up, and the goal of several clinical trials.

HUMAN SPACE FLIGHT. Out with the old, in with … to be determined. With the U.S. space-shuttle fleet slated to be mothballed in September 2010 after nearly 3 decades of service, President Barack Obama must pick NASA's next launcher capable of carrying humans. He could go with the current Ares rocket design, call for a variant based on an existing expendable launcher, or ask commercial companies for a cheaper option. Obama also plans to decide whether to shoot for the moon, an asteroid, or a martian moon in the next decade.

CREDITS (TOP TO BOTTOM): MAI/LANDOV; MIT

First X-ray Laser Shines

IN APRIL, A NEW TYPE OF LIGHT FLASHED INTO existence. Physicists at SLAC National Accelerator Laboratory in Menlo Park, California, turned on the world's first x-ray laser, a 130-meter beast called the Linac Coherent Light Source (LCLS) that is powered by the lab's 3-kilometer, straight-shot particle accelerator. The machine is the heart of a $420 million user facility, and after 3 years of construction, researchers needed less than 2 hours to fire it up.

The LCLS is a tool, but it deserves the appellation "breakthrough" because it takes a qualitative stride far beyond its predecessors. For decades, scientists have used x-rays to probe the atomic-scale structure of materials. Shining a billion times brighter than any previous source, the LCLS produces pulses of x-rays as brief as 2 millionths of a nanosecond, short enough to snap stop-action images of chemical reactions in progress. Simply put, the LCLS is the first device to combine atomic-scale spatial and temporal resolution. It also pumps out x-rays in a coherent quantum wave, allowing researchers to borrow techniques developed for conventional lasers.

Experiments with the LCLS began in October. Scientists hope to determine the structure of a protein from a sample of one molecule or rip out the inner-shell electrons from all the atoms in a material to see how the stuff reacts. Given that x-ray sources called synchrotrons are already workhorses for structural biologists and material scientists, some question what exactly the newfangled LCLS will be good for. But the fact that scientists are asking "What can we do with this?" shows that the LCLS is something completely new that may produce dramatic advances nobody has foreseen.

–THE NEWS STAFF

Beaming. Electrons zipping through the LCLS's magnets (*above*) generate copious x-rays.

CREDITS (TOP TO BOTTOM): PUBLIC HEALTH AGENCY OF CANADA; BRAD PLUMMER/SLAC

Near miss. The H1N1 virus was less virulent than feared, but the next pandemic could be worse.

SPECIALSECTION

VIRUS OF THE YEAR
THE NOVEL H1N1 INFLUENZA

FOR YEARS, SCIENTISTS HAVE BEEN WARNING THAT an influenza pandemic could strike at any moment, triggering a global catastrophe on the order of the 1918 Spanish flu. They imagined the culprit would surface in Asia—and, since 2003, have worried that the avian influenza strain H5N1 might be it. Health officials worldwide drafted one preparedness plan after another.

But the pandemic that erupted last spring looks nothing like the one in the plans. Not only did it begin in North America, but the swine virus behind it is a novel form of an H1N1 strain already circulating in humans. And although the new H1N1 is unusually dangerous for the young and for pregnant women, in most otherwise healthy people it causes a disease no more severe than seasonal flu. Scientists have repeatedly warned that this relatively mild virus could mutate or swap genes with cousins and become deadlier. But for now, it looks as if this H1N1, which mysteriously jumped from swine to humans, will go down in history more for causing confusion than catastrophe.

Not everything went wrong. The virus was discovered in humans earlier than it might have been, thanks to new technologies and border-surveillance programs set up in the wake of 9/11. Mexico, the hardest hit country, at first openly discussed its unfolding epidemic and mounted an aggressive response. Scientists characterized the new virus and distributed tests to detect it at record speed, sharing findings nearly in real time. Regulatory bodies rushed to approve new vaccines and drugs. And information campaigns, aided by the Internet, have kept the public apprised of the pandemic's course and of efforts to prevent and treat disease.

Yet the novel H1N1 virus ultimately revealed more weaknesses than strengths in the world's ability to combat pandemic influenza. As a symbol of the depth of the confusion, the World Health Organization (WHO) held an awkwardly prolonged backroom debate about whether the outbreak even merited the "pandemic" designation, and officials floated a cornucopia of names for the virus, none of which has stuck. But the problems were far more than symbolic.

Because of flimsy flu surveillance in pigs, the virus went undetected for years. By the time it was discovered, it had been circulating in humans for months—far too late to be contained with quarantines and antiviral drugs (stockpiled by WHO for that purpose), as mathematical models suggested could be done if a new pandemic virus were spotted early enough. Against the advice of WHO, many countries instituted useless travel bans and quarantines, and Egypt went so far as to kill all its pigs—even though not a single case of pig-to-human transmission had been found.

But the biggest wake-up call has been with vaccines, the cornerstone of pandemic preparedness plans. Almost as soon as the virus was isolated, public health labs and manufacturers kicked into high gear. Unfortunately, they hit one snag after another. Given the pandemic's April debut, no one expected the vaccine to arrive in time for the Southern Hemisphere's winter. But for the Northern Hemisphere as well, it came too little, too late. Most countries did not start vaccination programs until October or November, when the pandemic's second wave was in full swing.

The distribution of vaccines proved equally vexing. Despite lofty rhetoric at international meetings about global equity, poor countries were last in line. So far, WHO has received promises of a mere 200 million or so vaccine doses to help the poor, and delivery didn't start until early December. Moreover, the United States failed to stretch the supply of vaccines by using immune-enhancing adjuvants. European countries that did use adjuvants insisted on a two-dose regimen despite evidence that a single dose protects people over 10 years of age. So far, the global disparities have failed to ignite much political indignation. But if the new H1N1 had been a major killer, many public health experts believe the wealthy world's behavior would have created diplomatic mayhem.

Mistrust of the vaccine also reached a new high. Celebrities have denounced it, proudly proclaiming that they would not give it to their H1N1-vulnerable children—and many others have followed their advice. The Internet has fueled rumors about the vaccine, ranging from the simply false ("It hasn't been tested on humans") to the paranoid ("It's a WHO-led plot to depopulate the world").

In the final analysis, this anticlimactic pandemic might be best remembered as a trial run for the truly vicious killer that may come one day. And it has demonstrated that if influenza's Big One had struck in 2009, we would have been in a world of hurt.

–MARTIN ENSERINK AND JON COHEN

French science stimulus
1613

The threat from an Asian lake
1614

2010 U.S. BUDGET

Congress Takes Care of Science In Quiet Finish to a Busy Year

Congress has quietly passed a 2010 spending bill that gives several U.S. science agencies pretty much what they expected, including a 2.3% bump for the National Institutes of Health (NIH) and a 6.7% increase for the National Science Foundation (NSF).

The lack of fireworks stems in part from the lawmakers' preoccupation this year with other issues—from health care reform to the war in Afghanistan. But another factor was the $18 billion investment in research approved in February as part of the $787 billion stimulus package to revive the sagging economy (*Science*, 27 November, p. 1176). That windfall postponed until next year most of the usual battles over each agency's annual appropriations.

Acting last week only days before the expiration of a temporary spending extension, the House of Representatives and the Senate approved a $450 billion omnibus bill covering six of the 12 annual spending bills for the fiscal year that began on 1 October. In addition to NIH and NSF, the legislation funds the National Oceanic and Atmospheric Administration and the National Institute of Standards and Technology within the Department of Commerce. Several science agencies had already received their 2010 budgets in standalone legislation passed earlier this fall. At press time, Congress was still working on the final 2010 spending bill, which would fund the Department of Defense.

Within NSF's overall budget of $6.926 billion, legislators trimmed $115 million from a 10.5% increase requested for research activities, leaving it at $5.62 billion. Even so, they suggested that NSF seek additional time for U.S. astronomers on the twin Gemini telescopes in Hawaii and Chile built by a consortium of countries. They bumped up the Administration's requested 2% boost for education by $15 million, to $873 million, saying the extra money should be used to help elementary school students learn math and science.

Congress also took the unusual step of telling the White House that its request for 2011—to be unveiled on 1 February—should be larger than it had signaled last spring. A report accompanying the bill said that NSF needs at least a 7% boost if the agency's budget is to stay on track for a 10-year doubling by 2016. That calculation excludes $3 billion in one-time funding that NSF received from the stimulus package, most of it already allocated in grants that run for as long as 5 years.

The $692 million increase for NIH, to $31 billion, tops the Administration's $450 million request, which was low-balled because of the $10.4 billion in stimulus money that NIH received. Biomedical lobbyists were relieved that conferees dropped House-approved language removing funding for three NIH grants to study HIV risks among sex workers and alcoholics. A controversial $3 billion project to track the health of 100,000 children from the womb to age 21 received up to $194 million—enough to enable researchers to continue with a pilot study and prepare for a full launch in 2011.

Within NASA, legislators met the Administration's request for science, including $441 million to prepare the James Webb Space Telescope for a 2014 launch. But they called for a project review after noting a $95 million cost overrun in the past 6 months alone. Lawmakers provided $25 million to begin work on a replacement to the Orbiting Carbon Observatory, which landed in the ocean earlier this year, and set aside $15 million to start work on a robotic mission to Jupiter's moon Europa. They even asked NASA what it would cost to launch the Europa mission in 2018, 2 years ahead of the current schedule.

In October, Congress gave a 2.7% hike, to $4.9 billion, to the Department of Energy's (DOE's) Office of Science, which received a $1.6 billion infusion of stimulus money that it spent on "shovel ready" research projects and facilities. Legislators told DOE's new energy research agency, ARPA-E, to exhaust its $400 million in stimulus funding before asking for an annual appropriation. Toward that goal, agency officials this month announced a $100 million competition for far-out ideas to improve vehicular battery storage, carbon capture, and the conversion of carbon dioxide into liquid transportation fuels. ARPA-E's inaugural competition, which covered all aspects of clean energy, distributed $151 million to 37 grantees, leaving roughly $150 million for a third round sometime next year. **–JEFFREY MERVIS**

U.S. RESEARCH BUDGETS AT A GLANCE (IN $ MILLIONS)

Agency	FY '09 final	Stimulus package	FY '10 request	FY '10 final	Change from FY '09
National Institutes of Health	30,317	10,400	30,759	31,009	+2.3%
National Science Foundation	6,490	3,000	7,045	6,926	+6.7%
Research	5,183	2,000	5,733	5,618	+8.4%
Education	845	100	858	873	+3.3%
NASA science	4,503	400	4,477	4,469	–0.8%
Energy Dept. Office of Science	4,773	1,600	4,942	4,904	+2.7%
ARPA-E	0	400	10	0	
Commerce Department					
NOAA research	700	1	644	700	0.0%
NIST labs	644	580	652	662	+2.8%
EPA science	564	0	587	594	+5.3%
USDA competitive research	201	0	201	262	+30.3%
USGS research	612	74	649	660	+7.8%

Almost done. Last week's vote left the Defense Department as the only agency without a 2010 budget.

SOURCE: CONGRESS, AAAS; (PHOTOS) PHOTOS.COM

Toward a U.S. ocean policy

1618

Ecology meets genomics

1620

ACADEMIC FREEDOM

Terrorism Charges Against Grad Student Raise Questions

Last month a sociology graduate student at the University of Minnesota, Twin Cities, was charged with conspiracy under the Animal Enterprise Terrorism Act after he refused to testify before a grand jury that is apparently investigating a laboratory break-in at the University of Iowa in 2004. His academic adviser and 1600 others have signed an online petition urging the government to drop the charges against him, arguing that his academic freedom is at stake.

The student, Scott DeMuth, 22, studies radical activist groups. In the course of his research, he and his advisers say, he has promised confidentiality to his subjects. Compelling him to break this promise and reveal anything he might know about the Iowa raid—which caused more than $400,000 in damages—would violate social scientists' code of ethics, his supporters argue.

The case raises a number of questions, not the least of which is whether DeMuth is a promising young researcher trying to uphold the ethical standards of his field or an activist trying to use his academic ties as a cover for allegedly breaking the law.

In an interview with the Associated Press (AP), DeMuth denied that he was involved with the Iowa break-in or that he has ever been an animal-rights activist. DeMuth does, however, belong to Earth Warriors are OK!, a prisoner support group for people accused of illegal acts related to environmental and animal-rights activism, according to the AP and other sources. In an e-mail to *Science*, DeMuth defended his decision not to testify before the grand jury, but he did not respond to questions or requests for an interview.

As an undergraduate at the University of St. Thomas in St. Paul, Minnesota, DeMuth conducted research on the Minnehaha Free State struggle, a 1998 protest in which environmental and Native American activists camped illegally on land slated for a rerouted highway. DeMuth interviewed participants and presented his findings at meetings of the Midwest Sociological Society in 2008 and 2009, says his undergraduate adviser, sociologist Lisa Waldner.

Some of the activists involved in the Minnehaha protests have also been involved in public events supporting people jailed for animal-rights activities, says David Pellow, DeMuth's graduate adviser. "We're surmising that [the government] believes that from this project he may have interviewed people who were involved or know people who were involved in the Iowa vandalism," Pellow says.

Contempt of court. Scott DeMuth (*left*) and Carrie Feldman refused to testify before a grand jury in Iowa last month.

In mid-November, DeMuth and former girlfriend Carrie Feldman, 20, were subpoenaed to appear before a grand jury in Davenport, Iowa. Both refused to testify and were jailed for contempt of court. Two days later—just as the statute of limitations was expiring on the Iowa raid—DeMuth was charged with conspiracy under the Animal Enterprise Terrorism Act, a 2006 law that gives investigators and prosecutors more power in pursuing crimes by animal-rights activists. (DeMuth was released pending his trial; Feldman remains in jail but has not been charged.) The indictment doesn't mention the Iowa incident explicitly but lists a time period and location that match. Whether DeMuth stands accused of participating in the raid, helping to plan it, or playing some other role is unclear. Clifford Cronk, the assistant U.S. attorney involved with the case, said he was not permitted to comment.

A motion filed by Cronk to block DeMuth's release does mention the lab break-in and claims that FBI agents have found evidence that DeMuth is "an anarchist who has been engaging in illegal anti-government activities" and is "a part of the movement identified as the Animal Liberation Front," which claimed credit for the Iowa raid.

DeMuth's academic advisers paint a different picture. "He's a really bright young man," says Pellow. "He was a star undergraduate student, and he's got several projects … building on that work."

Pellow and Waldner argue that DeMuth's role as an activist shouldn't necessarily undermine his credibility. It's not uncommon for sociologists to participate in the groups they study, Waldner says: "Some people argue that participant observation is not a valid research strategy because of the objectivity issue. Other folks argue it's the only way to understand the viewpoint of the people you're trying to study."

The petition for DeMuth cites portions of the code of ethics of the American Sociological Association (ASA) that deal with confidentiality between researchers and subjects. The ASA has not taken a position on DeMuth's case, says the association's executive officer, Sally Hillsman: "We don't know enough about the specifics." But she adds that confidentiality is crucial for research in areas such as domestic violence, police brutality, and other illegal behavior.

However, she notes that conflicts can arise between the sociologists' code of ethics and legal obligations. Many sociologists avoid getting into a bind by telling subjects up front that they do not want to hear anything about future illegal activities, Hillsman says.

Those who choose otherwise may face consequences, and DeMuth seems determined to protect his sources, even if it means going to jail. The government's case against him should become clearer as his trial, scheduled for 1 March 2010, approaches. **–GREG MILLER**

CREDIT: EWOK

SCIENTIFIC INTEGRITY

A Dark Tale Behind Two Retractions

The notices published in *Science* last month and online in the *Journal of the American Chemical Society* (*JACS*) in September were brief: Two papers from a prominent chemistry lab were being retracted because the results couldn't be replicated. Part of the story behind the retractions is anything but straightforward, however. It involves an extortion attempt and a threat of suicide.

The papers were published in 2004 from the laboratory of Peter Schultz, a chemist at The Scripps Research Institute in San Diego, California. They extended pioneering work in Schultz's lab on a method for incorporating non-native amino acids into proteins (*Science*, 20 April 2001, p. 498). Conventional proteins are made up almost exclusively of 20 amino acids that are coded for by DNA, though hundreds of other amino acids occur naturally. Schultz and his colleagues offered biologists a way to incorporate some of these nonstandard amino acids, which could then serve as novel chemical handles to manipulate proteins of interest. Today, dozens of these chemical handles are used by everyone from drugmakers to cell biologists looking for new ways to understand how proteins function.

In 2004, Zhiwen Zhang, then a postdoc in Schultz's lab, and several other co-authors reported in *Science* that they had extended the technique to introduce an unnatural amino acid that came preloaded with a specific sugar group (*Science*, 16 January 2004, p. 371). Such sugar groups are common appendages on glycoproteins. But because the sugars are difficult to express uniformly and to purify, understanding their role has long been viewed as a major challenge. The *Science* paper offered researchers the possibility of systematically studying the effect of different ways proteins are modified. On 11 November 2004, Zhang, Schultz, and their colleagues published a second paper in *JACS* reporting the incorporation into a protein of a sugar-loaded amino acid that's a core unit in glycoproteins central to inflammation and cellular recognition.

At about the time of the *Science* paper, Eric Tippmann joined the Schultz lab as a postdoctoral assistant. Like Zhang, Tippmann worked on efforts to extend the technique of incorporating unnatural amino acids into proteins. A few months after Tippmann's arrival, Zhang left the Schultz lab to take a tenure-track position as an assistant professor of pharmacology at the University of Texas (UT), Austin. Tippmann says he became interested in Zhang's work because fellow students and postdocs told him they were having trouble replicating it. Tippmann says he reviewed Zhang's work closely in the fall of 2006. In September 2006, Tippmann spoke at a Schultz group meeting outlining reasons why he thought Zhang's work was likely incorrect.

Schultz says the concerns raised were serious enough that he asked a group of lab members to try to replicate the work in Zhang's *Science* paper in addition to several other important discoveries Zhang had made. That task, however, was complicated by the fact that Zhang's lab notebooks, describing his experiments in detail, were missing. Schultz says that in the early fall of 2006, the notebooks were in Schultz's office. But at some point after that they were taken without his knowledge and have never resurfaced.

After considerable effort, Schultz says his students were able to replicate most of the work. The biggest exception was the work that served as the basis for the 2004 *Science* and *JACS* papers. "It was clear the glycosylated amino acid work could not be reproduced as reported. So we tried to figure out what was going on," Schultz says.

In the midst of this process, events took an ominous turn. On 1 March 2007, Zhang received an e-mail that listed the author as "michael pemulis," who claimed to have discovered "fraud" in multiple papers. If Zhang did not send $4000 via overnight mail to a post office box in San Diego, the e-mail sender said he or she would reveal this "fraud" to faculty at Scripps and UT Austin. "They will investigate you. … pete will retract all your post-doctoral work. you lose job. … Texas will fire you before you tenure," the e-mail states.

No longer valid. Papers in *Science* (*above*) and *JACS* (*left*) were retracted when the work could not be replicated. It now appears that the problem may be with an enzyme that resulted in false positives.

"I was scared to death," Zhang recalls. He immediately contacted Schultz, who in turn contacted Richard Lerner, president of Scripps. At Lerner's urging, Schultz and Zhang then contacted the San Diego Police Department, which forwarded their case to its electronic crimes unit. About a month later, in April 2007, Zhang says the officer in charge of the case told him that they had a suspect and asked whether he wanted to press charges. Zhang says he decided not to do so in hopes the situation would blow over.

It didn't blow over. In November 2007, an anonymous letter was sent to officials at several institutions, including Scripps; UT Austin; the University of California, Berkeley; and *Science*'s editorial department. The letter stated that it was from "a member of PGS [Peter G. Schultz] lab" and called the 2004 *Science* paper a "fake." "I feel like leaving science or committing suicide," the letter stated. Zhang says that when he saw the letter, "my jaw dropped again."

The disturbing events haven't stopped. Zhang says over the past 2 years, he has received several anonymous phone calls at his UT Austin office phone number in which the caller hasn't said anything and then hangs up. Zhang says he's tried calling the number that pops up on his caller ID, but a recording on the other end says it is a long distance calling card center in Mississippi. Zhang says he and his family have become unnerved: "We don't feel safe anymore." The stress has gotten so high, that his wife and children moved away from Texas some time ago and have since been in virtual hiding. "It's horrible," Zhang says. "I'm just trying to be a good scientist. This is not science."

The events, Schultz says, affected him deeply as well. "It put me in a situation where I

felt there was an extra burden on me to find out what was going on, given the threats," he says. Today, after years of effort, Schultz says he feels he and his students are starting to understand what may have gone wrong with the original experiments. Although still preliminary, it appears that the problem might be with the enzyme that they thought was binding to the unnatural amino acid and incorporating it in the protein. A test with a different glycosylated amino acid shows that it actually binds the unnatural amino acid not in the normal "active site" but at another site. Here it then prompts a conventional natural amino acid to be incorporated in the active site, giving a false positive reading. In the end, Schultz says, Tippmann was right to have doubts. "There was something wrong with the work."

That meant the *Science* and *JACS* papers needed to be retracted. Zhang says Schultz contacted him in July and suggested that the papers be pulled. Zhang was preparing for his tenure review at UT Austin and says he was concerned that retracting the papers would prove damaging to his chances of receiving tenure. Nevertheless, after Schultz and Zhang talked it over, they agreed to retract both papers. After receiving signed agreement from each of the authors, a process that took several weeks, Schultz sent the retractions to *Science* and *JACS* on 11 August.

JACS quickly accepted the retraction. But editors at *Science* informed Schultz that the journal's editorial practice requires that they get signatures directly from all authors wishing to retract a paper. During that process, Zhang informed *Science*'s executive editor, Monica Bradford, of the extortion e-mail and the missing lab notebooks. In response, *Science*'s editor-in-chief, Bruce Alberts, called Schultz to suggest that the retraction letter in *Science* should state that the lab notebooks were missing through no fault of the authors; that wording helped explain why they had trouble replicating the experiments. In the end, the retraction was published on 27 November.

The summer brought other developments. On 7 August, Tippmann, now a lecturer at the University of Cardiff in the U.K., co-authored a paper that laid out several reasons why Zhang's original glycosylated amino acid experiments could not have worked. And in October, Zhang was told he would be denied tenure by UT Austin. For his part, Tippmann says he's sorry that Zhang has had to undergo this ordeal, but that his involvement has been entirely limited to the science, and he had nothing to do with the missing notebooks, the March 2007 e-mail sent to Zhang, or the November 2007 letter. Schultz says he and his Scripps colleagues will continue to search for answers. Lerner concludes: "There was somebody who did this, really turned lives upside down, and made doing science a lot harder than it had to be." **–ROBERT F. SERVICE**

"There was somebody who did this, really turned lives upside down, and made doing science a lot harder than it had to be."

—RICHARD LERNER, SCRIPPS RESEARCH INSTITUTE

With reporting by Michael Torrice.

U.S. SCIENCE POLICY

Chair of Science Panel to Leave Congress

CREDIT: U.S. CONGRESS

Saying that "it's time to do something else," the chair of the House Science and Technology Committee announced this week that he will retire at the end of 2010. Ending a 26-year career in Congress, Representative Bart Gordon (D–TN) leaves Democratic Party leaders scrambling to defend a seat in a Republican-leaning district and research lobbyists wondering how his successor will take to the role of spokesperson for science.

The 60-year-old Gordon, who joined the committee as a freshman in 1985 and has been chair since 2007, helped turn a 2005 National Academies report into 2007 legislation that has provided a blueprint for research and education programs at the Department of Energy and the National Science Foundation. He says reauthorizing the America COMPETES Act next year is his highest priority.

The second-ranking Democrat, Representative Jerry Costello (D–IL), has already declared his interest in becoming chair. One of the less-visible members of the committee, Costello has been active on national transportation issues and has championed the FutureGen carbon sequestration and storage project in his southwestern Illinois district. **–JEFFREY MERVIS**

ScienceNOW.org

From *Science*'s Online Daily News Site

HIV Outwits Yet Another Microbicide
The largest study ever conducted of a microbicide designed to prevent HIV infection has resulted in yet another case of high hopes being dashed about a promising product. Earlier in the year, a smaller study of the same vaginal gel gave a hint that it might offer modest protection, but the new results put the question to rest. http://bit.ly/hivgel

A Cheap Way to Chop Up Nitrogen
Nitrogen atoms are needed to make many important chemicals, from drugs to fertilizers. But getting those atoms into chemicals is challenging because nitrogen molecules are tough nuts to crack. They consist of two atoms sharing a stubborn triple bond, which chemists can break up only by scorching them with temperatures of up to 500°C. And that results in the simple chemical ammonia, which needs further processing to produce more complicated compounds. Now chemists have devised a new way to split molecular nitrogen and synthesize a common fertilizer. http://bit.ly/nitrogen

A Mind That Touches the Past
Imagine planning your schedule for the week and seeing the days on the calendar appear before you as a spiral staircase so real you feel like you could touch it. That's what it's like to have spatial-sequence synesthesia, a condition in which people perceive numbered sequences as visual patterns. Now researchers have shown that individuals with the condition have superior memories, recalling dates and historic events much better than the average person can. http://bit.ly/time-space

Better Nanotubes May Be on the Way
In the world of nanotechnology, few things get as much billing as nanotubes. Experts say that these cylinders composed of one-molecule-thin sheets could someday be used in everything from superstrong jet engines to cancer cures. Now researchers think they've found a way to make large amounts of an elusive type of nanotube that could provide even more impressive applications. http://bit.ly/bnnt-nanotubes

Read the full postings, comments, and more on **sciencenow.sciencemag.org**.

EVOLUTION

Spineless Fish and Dark Flies Prove Gene Regulation Crucial

Almost 3 years ago, biologists got into a tussle over what drives morphological evolution: changes in the protein-coding portions of genes or changes in the DNA regions that regulate gene activity. At the time, some researchers felt there was little hard evidence to support the idea that regulatory changes were indeed important (*Science*, 8 August 2008, p. 760).

Now, on page 1663 and in last week's *Science* Express (www.sciencemag.org/cgi/content/abstract/science.1182213), two teams not only independently report that changes in regulatory DNA were responsible for an adaptation in natural populations of fish and insects, but each group has also pieced together details of the underlying genetic alterations in those animals. "They provide beautiful and convincing examples of how [certain] regulatory elements can be lost or modified to reduce [gene] expression, ultimately causing morphological change," says Hopi Hoekstra, an evolutionary biologist at Harvard University and one of the chief skeptics.

Color coordinated. In Africa, lowland fruit flies are light-colored, whereas those at high altitudes are dark, all because of a change in gene regulation.

In one case, the same piece of regulatory DNA was lost in different freshwater fish populations, each time causing the loss of pelvic spines. In the other case, the darkening of a fruit fly took place through an accumulation of small mutations in regulatory DNA. Taken together with other discoveries of noncoding regions involved in evolution, "there is broad support now" that changes in regulatory DNA can generate morphological variation, says Günter Wagner, an evolutionary developmental biologist at Yale University.

The fish study took place at Stanford University, where David Kingsley has spent the past decade tracking down the genetic basis for why three-spined sticklebacks (*Gasterosteus aculeatus*) that live in salt water have spines jutting from their belly whereas some of their freshwater counterparts do not. In salt water, the pelvic spines help make the stickleback difficult for a predator to swallow, but the protuberances become a hindrance in fresh water as they could serve as handholds onto which dragonflies and other carnivorous insects grab.

In 2004, Kingsley and his colleagues tracked the disappearance of the pelvis in multiple populations of freshwater sticklebacks primarily to a gene called *Pitx1*. The gene is expressed during development in many places in both fish types. But it's active in the pelvic region of the saltwater animals and not in the freshwater ones, Kingsley's team found. Yet the gene's coding region is virtually unchanged between fresh- and saltwater fish, suggesting regulatory DNA is the difference.

The new work confirms that suspicion. When Kingsley, his graduate student Yingguang Frank Chan, now at the Max Planck Institute for Evolutionary Biology in Plön, Germany, and their colleagues studied fish with and without a pelvis, they determined that DNA upstream of *Pitx1* was responsible for silencing the gene. They broke that DNA into fragments and determined exactly which piece, an enhancer called *Pel*, turned *Pitx1* on in the pelvis. When the researchers compared the sequence of *Pel* in saltwater sticklebacks and freshwater ones from nine different lakes, they found the latter populations each had various amounts of missing DNA bases in the enhancer region, including an apparently key 488-base region that is absent in most of the lake fish.

"The fact that multiple alleles, with unique mutations, were observed is surprising and emphasizes the tinkering nature of the evolutionary process," says Patricia Wittkopp, an evolutionary biologist at the University of Michigan, Ann Arbor.

To confirm *Pel*'s importance, the researchers added a saltwater stickleback's version of the enhancer and *Pitx1* to the fertilized eggs of freshwater sticklebacks that don't normally sport pelvic spines. The resulting transgenic freshwater fry developed the structures.

For the insect study, evolutionary biologists Sean Carroll and Mark Rebeiz of the University of Wisconsin, Madison, and their colleagues followed up on work into why the normally yellow abdomens of fruit flies (*Drosophila melanogaster*) have become dark in some African populations living at high elevations. Earlier work done by collaborators John Pool of the University of California, Berkeley, and Charles Aquadro of Cornell University suggested that this color change was due to a change in the activity of a gene called *ebony*.

The new work narrows down the cause to an enhancer upstream of the gene. By dissecting the function of this region in different *Drosophila* populations, ones with either dark or light abdomens, the researchers identified five mutations that reduced *ebony* expression to varying degrees.

Three of those mutations are present in *Drosophila* with light abdomens, but the dark flies from high altitudes also have two newer mutations. These two have the biggest effects on squelching *ebony* expression, but all five mutations combine to create the full color change.

The work "leads to two very important conclusions about classic evolutionary genetic questions," says William Cresko, an evolutionary biologist at the University of Oregon, Eugene. One is that a "big" evolutionary step—a color change—actually can come about because of several little steps: multiple mutations in the enhancer. Secondly, it shows that adaptive mutations sometimes exist unnoticed in a population.

Others are also in hot pursuit of evolutionary changes based on regulatory elements. Wittkopp is homing in on mutations in a regulatory region that change body color between two closely related species of fruit flies (*Science*, 23 October, p. 540). And Hoekstra's group has a regulatory region in its sights that seems to underlie mouse color changes (*Science*, 28 August, p. 1095). But developing a broad understanding of the relative roles of shifts in gene regulation versus changes in the proteins encoded by genes "will require many more case studies from across a wide array of taxa," cautions Cresko. Given how much work the two new studies took, he adds, it may require a "quantum leap" in technology for that to be possible.

–ELIZABETH PENNISI

CREDIT: MARK REBEIZ *ET AL.*, *SCIENCE*

FRANCE

Sarkozy's 'Grand Loan' Bets That Research Will Pay Off

PARIS—On Monday, president Nicolas Sarkozy announced a €35 billion investment plan that he pledged would make France's science more productive, its population smarter, its economy more competitive, and its environment cleaner. The plan was originally envisioned as an economic stimulus similar to the one passed by the United States earlier this year but has been rebranded as an investment in the "France of tomorrow" because Sarkozy is betting heavily on research, higher education, and innovation. It sets aside almost €8 billion to establish a handful of elite academic centers, and €3.5 billion for turning research into products and services.

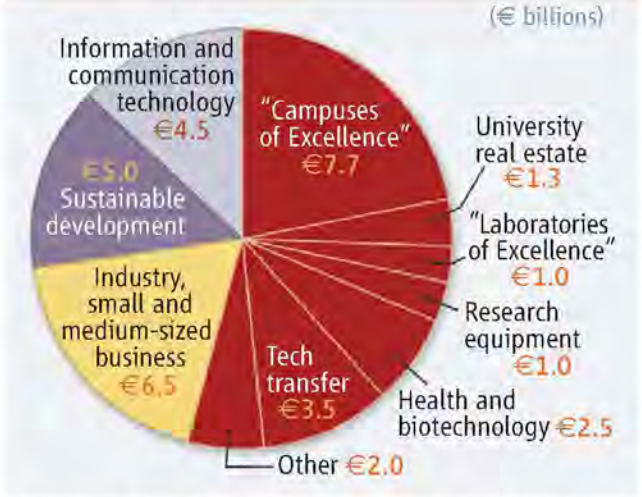
Almost two-thirds of the €35 billion will be borrowed money—hence the nickname the "Grand Loan"—and economists have warned that Sarkozy is imperiling France's long-term fiscal health. Some researchers, meanwhile, dismiss the plan as a PR stunt. Most of the money will be in the form of capital endowments to universities from which they can only use the annual interest. Thus, the net increase for science is several hundred millions of euros annually, says physicist Bertrand Monthubert, secretary-general for research and higher education in the minority Socialist Party. That's barely enough to offset years of neglect, says Monthubert, who calls the plan "a mirage."

Sarkozy largely followed recommendations issued in November by a panel chaired by two former prime ministers, socialist Michel Rocard and conservative Alain Juppé. The stimulus plan's centerpiece are endowment-style funds for five to 10 "Campuses of Excellence," to be selected by an international jury and modeled on academic hotbeds in the United States. Each will consist of a number of universities, research institutes, and so-called Grandes Écoles in close geographical proximity; they are expected to work closely together or even merge. One explicit goal is to create universities that score better in controversial academic charts such as the Shanghai ranking. France's poor showing is a source of political embarrassment. "The goal is simple: we want the best universities in the world," Sarkozy said on Monday during a press conference from the Elysée Palace.

The endowments will allow the chosen universities to attract top talent by making long-term funding commitments, says Alain Beretz, president of the University of Strasbourg. But critics worry that dozens of smaller, regional universities will be left by the wayside. "It's fine to have a pyramid, but you can't ignore the base," says Laurent Bouvet of the University of Nice, who specializes in—and blogs about—higher education policy. Sarkozy's plan does reserve €1 billion for "laboratories of excellence" outside the elite; universities were hoping for more, says Lionel Collet, president of the University of Lyon 1 and chair of the Conference of University Presidents.

In his speech, Sarkozy tried to reassure financial markets and the European Union that the country's debt won't spiral out of control. On the contrary, he said, the Grand Loan will result in a more competitive economy and a healthy tax revenue stream.

SARKOZY'S INVESTMENT PACKAGE



Hey, big spender. More than half of the €35 billion package will directly benefit research and higher education (shown in red).

Indeed, the plan puts a strong emphasis on technology transfer, an area in which France is lagging. There will be a €1 billion national fund to help exploit publicly funded science and €2 billion for new technology innovation institutes. Research would also benefit from other parts of the plan; a €5 billion investment in "sustainable development," for example, will promote so-called fourth-generation nuclear reactors and alternative energy sources. **–MARTIN ENSERINK**

CREDITS (TOP TO BOTTOM): PHOTOS.COM; PHILIPPE WOJAZER/REUTERS/LANDOV; OFFICE OF THE FRENCH PRESIDENT

*Science*Insider

From the *Science* Policy Blog

The world may be focused on Copenhagen this week, but next spring all eyes will be on the U.S. Senate as it gets down to brass tacks on climate change. This week's *Science*Insider offers a comprehensive look at the **political climate for that debate**—interviews with the key players, analysis of the biggest issues, and a look at where the votes are. Learn whether the so-called world's greatest deliberative body may take meaningful steps to reduce global warming. http://tinyurl.com/climatesenate

Ireland's funding allocation for science, technology, and innovation is being cut by 4.4% in 2010. And in a major change of policy, research will be funded through a single stream from one government department. http://tiny.cc/6UYy9

Harvard University is temporarily halting construction on a $1 billion **life sciences complex in Allston**, several kilometers away from the main Cambridge campus. http://tiny.cc/GS0xV

In a continuing battle with the facility's governing board, scientists at the **Australian Synchrotron are again working on a 9-to-5 schedule** rather than around the clock. The partial strike could severely hamper research efforts. http://tiny.cc/2q6DH

U.K. Science Minister Paul Drayson announced that Britain will **create its own space agency**. No news yet on the body's name or spending power. http://tiny.cc/KKNlp

Carlos Pérez del Castillo, a career civil servant from Uruguay, **was named chair** of the new board of the Consortium Board of the Consultative Group on International Agricultural Research Centers, a network of 15 agricultural research organizations from around the world. http://tiny.cc/dLvXz

For these stories and more, go to **blogs.sciencemag.org/scienceinsider**.

Alpine jewel. Lake Sarez, formed a century ago by a landslide, now holds 17 cubic kilometers of water.

Peril in the Pamirs

Concerns about the risk of a calamitous flood from a mountain lake in Central Asia have scientists racing to improve evacuation plans and find an engineering fix

DUSHANBE—Once a month, Kadam Maskaev flies by helicopter to Lake Sarez, a jewel high in the Pamir Mountains in western Tajikistan. "Just knowing that nature is creating this wondrous lake before our eyes—it's a kind of magic," he says. Sarez *is* special, but there's nothing mystical about it, and Maskaev is no starry-eyed pilgrim. He's deputy director of Tajikistan's emergency situations committee, and Sarez is his chief concern.

The lake was born nearly a century ago, when a mountainside crumbled during a magnitude-7.4 earthquake. The 567-meter-high landslide blocked an alpine river, forming the world's tallest dam. Since then, the valley behind it has filled with 17 billion cubic meters of snow and glacier melt. Maskaev and others fear that the natural dam could someday give way, unleashing a wall of water from the 56-kilometer-long lake on villages along the Bartang and Panj rivers and the great waterway they feed: the Amu Darya, Central Asia's largest river.

The possible trigger for such a catastrophe would be another major earthquake shaking the region. A large temblor is virtually certain: The Pamirs are a seismic hot spot, and a quake of magnitude 7 or greater rattles the faults around Sarez every century or so. But a severe jolt in itself almost certainly would not directly bring down Usoi Dam, named after a village buried in the landslide on 18 February 1911. The scenario that Maskaev and other scientists worry about is a landslide into the lake, which could trigger a tsunami-like wave that would flow over and perhaps breach the dam. Just such a disaster claimed about 2000 lives in Italy in 1963. Scientists concur that the probability of a reprise at Sarez is low. But the consequence "would be a catastrophe," says Sharifov Gul, a chief engineer in Tajikistan's water ministry.

Adding uncertainty over how much force Usoi might withstand, a few years ago water began trickling in greater volumes through the upper part of the dam. That reassures some experts and unsettles others. "In the short term, that may relieve pressure. But in the mid- to longer term, it could have a destabilizing impact by increasing fissures in the dam," says Igor Zonn, director general of the Engineering Research Center on Water Management, Land Reclamation, and Ecology "Soyuzvodproject" in Moscow. "In either scenario," Zonn contends, "the risk remains high for settlements downstream."

With the sword of Damocles hanging over as many as 5.5 million people in the Amu Darya basin—including settlements in eastern Tajikistan and northern Afghanistan, Turkmenistan, and Uzbekistan—authorities are taking no chances. Tajikistan has installed a sophisticated warning system at Sarez, and officials throughout the region are crafting evacuation plans. The countries have their work cut out for them. "I'm not aware of any regional preparedness plans which would adequately address the potential risks," says Sergei Vinogradov, an expert on water law at the University of Dundee in the United Kingdom.

Reducing the threat is a daunting challenge. Shoring up Usoi Dam is not feasible, experts concluded at a workshop last September in Nurek, Tajikistan's gateway to the Pamirs. Rather, they agreed on the urgent need to draw down the lake, which last year reached its highest-ever water level. "The overwhelming international scientific consensus is that to guarantee long-term safety of the dam and lake, the water level should be reduced by 50 to 100 meters," says Roger Roschnik, a project manager at Stucky, a company in Renens, Switzerland, that developed the warning system. Several ideas have been floated for lowering the waterline. Meanwhile, researchers have proposed taking cores from Usoi. "Nobody knows what the dam looks like inside," says Maskaev. Scientific drilling, proponents say, would allow more robust estimations of the structure's stability.

As experts mull next steps, Maskaev's team is hewing to its prime directive: keeping vigil as the waters of Sarez rise.

One family's nemesis

Scientists have cast a wary eye on Sarez from the start. In 1913, Russian engineers dispatched to the disaster zone found the Murghab River backing up behind roughly 2 cubic kilometers of rubble, a pile of mostly shale and sandstone nearly three times as tall as the Hoover Dam on the Colorado River. The team enlisted a local man,

CREDIT: COURTESY OF KADAM MASKAEV

Keeping vigil. Tajik scientists monitor Sarez around the clock from the Dam House (*left*). A research team inspects the lake's underwater terrain.

Kabul Kurbonbekov, to monitor the newborn lake, which had already submerged the village of Sarez in the summer of 1912. The post of chief observer has passed from one generation to the next and now belongs to Kurbonbekov's great-great-grandson: Maskaev.

Concerns about Usoi's integrity have waxed and waned. An early fear was that a large earthquake would cause the 5-kilometer-long dam to fail. Most experts now discount that prospect. Usoi is stronger than any humanmade dam, calculations suggest. "I consider the dam safe, taking into account its dimensions and the time it has had to consolidate," says geologist Jean Schneider of the University of Natural Resources and Applied Life Sciences in Vienna.

The trouble spot, researchers say, is not Usoi but an unstable slope along Lake Sarez about 4 kilometers east of the dam. Imperceptible to the naked eye, a section of the lake's right bank is slipping about 10 centimeters a year toward the lake. There is a "relatively high possibility" that a strong earthquake would trigger a sudden collapse as the bank's saturated underwater portion liquefies in the shear zone, sending tens to hundreds of millions of cubic meters of debris plunging into Lake Sarez, says Kyoji Sassa, a disaster prevention specialist at Kyoto University in Japan and executive director of the International Consortium on Landslides.

The displacement would create a seiche wave, a kind of tsunami observed in lakes and other enclosed basins. A seiche wave at Sarez could wash over Usoi Dam, whose crest at its lowest point now sits only 38 meters above the lake's surface, says Sassa.

Just such a disaster occurred in Italy on the evening of 9 October 1963, when heavy rain triggered a massive landslide into a reservoir behind Vajont Dam north of Venice. The debris spawned a towering seiche that sent some 50 million cubic meters of water spilling over the 262-meter-high dam. The torrent, abetted by the tornado-force blast of air it displaced, obliterated five villages in its path.

The situation in Tajikistan is not nearly as precarious as it was in Italy. The reservoir's banks at Vajont were crumbling before the tragedy, suggesting that the terrain was unstable. Even if a major earthquake were to collapse Sarez's right bank, some researchers say the odds are against a disastrous seiche. "The probability is 1 in a million," asserts Jörg Hanisch of JorgeConsult in Hannover, Germany, who served on a panel that oversaw installation of the Stucky monitoring system by FELA Management in Diessenhofen, Switzerland. "The risk of even a partial outbreak is exaggerated," adds Schneider. "The dam will only possibly be overtopped in the far future." But Sassa and others argue that the threat is significant. The nightmare scenario is that the force of a tremendous seiche (the one at Vajont was approximately 250 meters tall) could breach and sweep away a large chunk of Usoi Dam—releasing, in minutes, much of Lake Sarez.

"Ten years ago, I was not as concerned about the risk of Usoi failing," says Maskaev. Since then, two things have changed. The 9/11 attacks revealed a vulnerability of any dam: Terrorists could blast a hole in Usoi with a hefty, well-placed bomb or by ramming a plane into it. Then in 2004, Maskaev's team noticed a marked increase in water seeping through the dam some 100 meters below the lake's surface.

The water is clear, which means it's not washing out debris and is unlikely to be weakening Usoi. "Internal erosion can be excluded," says Hanisch, who notes that such seepage is necessary for long-term stability of natural rockslide dams. Maskaev has a different take: "The filtration regime of the dam is changing, and that makes me nervous."

Planning for the worst

Whatever goes down at Lake Sarez, Maskaev's team will be the first to know. A five-person detachment keeps an eye on the lake around the clock from a station anchored with steel cables to a stable perch 150 meters above Usoi—out of the path of any seiche. "It's a perfectly safe place," Maskaev says.

Instrumentation has improved considerably since Great-Great-Grandpa Kurbonbekov's day. Stucky's $2 million monitoring system features strong-motion accelerographs for detecting tremors, GPS to track

Continued on page 1617

CREDITS (TOP TO BOTTOM): ADAPTED FROM GOOGLE; COURTESY OF KADAM MASKAEV

Apocalypse now. The Aral Sea's retreat left fishing boats adrift in sand.

Burdened by Soviet Legacy, Nations Spar Over Water Rights

DUSHANBE—As scientists worry about the prospect of a catastrophic flood from Lake Sarez in the Pamir Mountains (see main text, p. 1614), agricultural communities on the plains below face a very different problem. This arid region in Central Asia has inherited a set of resource blunders made decades ago by the Soviet Union. And since the Soviet collapse in the 1990s, competition for fresh water has increased. The situation might be eased, experts say, if Lake Sarez could be tapped and its surplus water distributed. But that won't happen anytime soon. For now, regional water problems are growing more intense.

Water scarcity is not the only woe. The people of Ferghana Valley in northwest Tajikistan are trying to bail out of a vast inundation, the belated consequence of a Soviet project called the Kayrakkum Dam, completed in 1956. As its reservoir filled, the water table of the surrounding land rose, infiltrating homes and spoiling crops. Engineers installed a drainage system to pump water back into the Kayrakkum reservoir. But now many of the pumps have broken down. Across 30,000 waterlogged hectares, sewage is backing up, salt has risen to the surface and is ruining fields, and homes are riddled with mildew, says civil engineer Akhrorov Akhatjon of the Ferghana Valley Water Resources Management Project. "The problem is getting worse," he says. The government lacks the resources to fix the drainage system, and villagers are too impoverished to relocate. A handful of people have had the means to rebuild homes on 3-meter-high foundations, but most simply endure the swampy conditions. "We're worried about the disease risk of poor sanitation," Akhatjon says. "It's a perilous situation."

Along the Tajik-Uzbek border, meanwhile, a perpetual squabble over water and energy resources is growing tenser. In winter as hydropower reservoirs in Tajikistan drop too low to generate power, Uzbekistan has accused Tajikistan of siphoning electricity from Central Asia's shared grid. This month, Uzbekistan pulled out of the grid—a move that has provoked talk of retaliation. "If [Uzbeks] don't want to give us electricity during winter, why should we give them water?" asks Sharifov Gul, a chief engineer in Tajikistan's water ministry.

Turning off the spigot is easier said than done. The source of most of Central Asia's water is rivers flowing from glacier fields in mountainous Kyrgyzstan and Tajikistan. There's little now that either country can do to stem the flow into Kazakhstan, Turkmenistan, and Uzbekistan. But that could soon change. Tajikistan is building the world's tallest artificial dam, Roghun, on the Syr Darya River. The 3.6-gigawatt hydropower station would make Tajikistan self-sufficient in electricity. Uzbekistan has opposed the 335-meter-high dam, arguing that Tajikistan might use Roghun to restrict downstream releases. That could devastate agriculture in Uzbekistan, whose cotton and wheat fields depend on irrigation from the Syr Darya and the Amu Darya. Gul insists that's not Tajikistan's intention: In fact, he says, Roghun could supply electricity to neighboring countries.

The most notorious example of poor management, perhaps, is the diversion of water a half-century ago from the Amu Darya and Syr Darya to irrigate cotton fields in Turkmenistan and Uzbekistan. The irrigation canals constantly hemorrhage water through their beds, while a substantial fraction of water also evaporates. By the 1970s, the Amu Darya no longer reached the Aral Sea. The shrinking sea grew saltier and fisheries were devastated; a Kazakh effort is replenishing part of the sea (*Science*, 14 April 2006, p. 183).

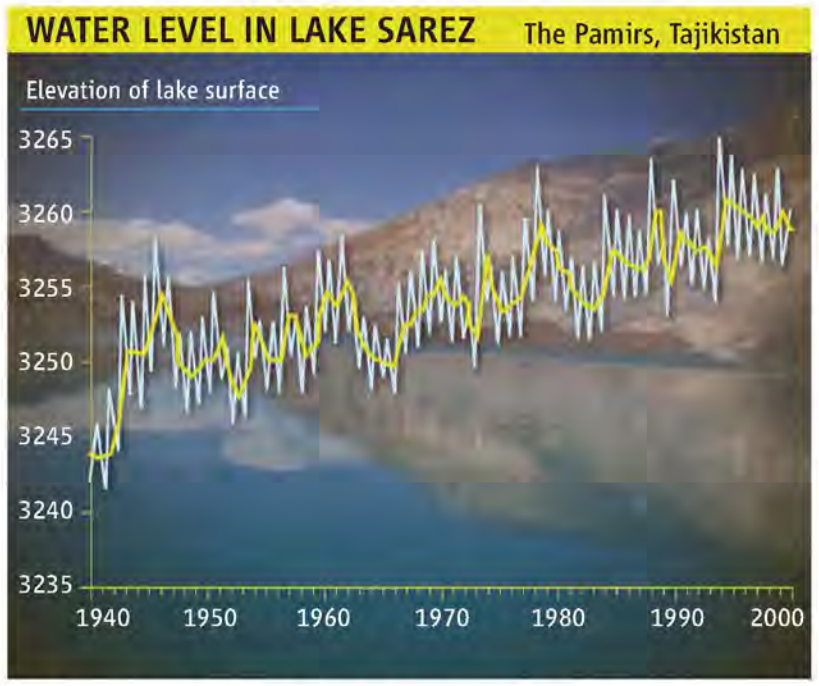
A fresh concern is the retreat of Central Asia's glaciers as temperatures rise. Both the Amu Darya and Syr Darya depend on glacier runoff to provide a stable flow in summer, says Daene McKinney, a civil engineering professor at the University of Texas, Austin. "Decreased glacier mass will likely cause this high level of dependable base flow to become more erratic, requiring more efficient water management," he says. The Amu Darya is expected to be the hardest hit, says Victor Dukhovny, director of the Scientific Information Centre of the Interstate Commission for Water Coordination of Central Asia in Tashkent. As a result, he says, there is already a "strong movement to water saving."

In a taste of hardships to come, Central Asia experienced a prolonged drought last year that resulted in water shortages. In response, Tajikistan stepped up construction of Roghun, a project started by the Soviets in the 1970s. It spent $150 million this year and plans a similar expenditure in 2010, and now has a 7000-strong work force at the site. To speed up the project, Tajikistan President Emomali Rahmon this month called on every Tajik family who could afford it to buy shares in Roghun.

The most urgent need at present, argues Dukhovny, is stronger water governance to mediate the struggle between hydropower companies intent on controlling water and agricultural concerns that have an inalienable right to water. Ministers of Central Asian nations meet every 3 months to discuss how to divvy up water under an existing treaty. But as resources grow scarcer, transboundary disputes are bound to grow more frequent. Because "international water law is very weak," Dukhovny says, it might take the intervention of the U.N. Security Council to forge a lasting solution. **–R.S.**

CREDIT: MUTSUMI STONE

Danger zone. Scientists fear that if an earthquake triggers a massive landslide into Sarez, the resulting tsunami could overtop and possibly breach Usoi Dam.



Tale of the tape. Sarez is rising gradually, but in the absence of a major temblor, it would be decades before water spills over the dam.

Continued from page 1615

movements of the right bank and the dam, and radar and pressure-cell sensors to monitor water levels in Sarez and in the Bartang River, downstream of Usoi. Although data are beamed by satellite to Dushanbe, a decision to evacuate would not wait for word from Tajikistan's capital. The warning system would trip if its detectors registered, for instance, a magnitude-5 or greater earthquake, a 25-centimeter rise in Sarez's level over 24 hours, or a 1-meter surge in the Bartang River below the dam.

Sirens would sound in 17 villages, and the residents of Barchidiv, the village nearest the dam, would have 17 minutes—"enough time," Maskaev assures—to reach provisioned shelters on higher ground. As they grab their children and food, villagers would listen for a radio advisory confirming a real emergency.

The Bartang valley population "is very well prepared and has gone through a number of evacuation drills," says Goulsara Pulatova, senior adviser to the U.N. International Strategy for Disaster Reduction's office in Dushanbe. Further downstream, however, preparedness falls off sharply. In Soviet days, evacuation plans were drawn up for settlements along the Amu Darya, all the way to the Aral Sea, says Maskaev. Renewed concerns over Sarez have prompted officials to dust off and revise these plans. Last summer, for instance, Termez, a major city in Uzbekistan on the Afghan border, held an evacuation drill. The conference in Nurek drew experts from Turkmenistan, which for years hadn't dispatched delegations to Sarez workshops, and from Afghanistan, which is seeking to set up a warning system on its side of the border.

Evacuation plans alone are insufficient for addressing the threat, cautions Michael Glantz of the University of Colorado, Boulder. Another need, he says, is contingency plans for rehabilitation and reconstruction in the event of a disaster. In addition, he says, Tajikistan may want to consider moving people permanently out of harm's way.

Waiting game

Experts have for now ruled out buttressing Usoi against a seiche. A more promising idea, they say, is to partly drain Sarez. If the lake level were lowered several dozen meters, says Hanisch, "even the highest imaginable wave could not overtop the dam."

Finding an engineering solution is easier said than done. The "best option," according to Sassa, is to tunnel through bedrock on Sarez's left flank and drain lake water via a conduit. Bearing in mind the immense pressure of 6 trillion tons of water, "it would require some very careful engineering to ensure a controlled release of water and that things didn't get out of control," says Philip Micklin, a geographer at Western Michigan University in Kalamazoo.

The project's estimated $500 million cost could be defrayed by building a 250-megawatt hydropower plant where water exits the tunnel. "Such a project would contribute to the social and economical development of the region," says Roschnik, who notes that Stucky is conducting a feasibility study with the World Bank's International Finance Corp.

Tapping Sarez could also defuse mounting tensions over regional water supplies in Central Asia (see sidebar, p. 1616). At the World Water Forum in Istanbul last March, Tajikistan President Emomali Rahmon proposed establishing an international consortium to construct a pipeline from Sarez to neighboring Uzbekistan. "Sarez has enough volume to provide drinking water for all of Central Asia," says Gul. A consortium has yet to materialize. "So far it's all just talk," Gul says. "The main problem is money."

An alternative strategy would be to construct a spillway, similar to one that army engineers in Pakistan built to drain a lake formed by the Hattian Bala landslide, a 68-million-cubic-meter rockfall set off by the 2005 earthquake in Kashmir. Such a trench, however, would dramatically increase the hazard of a seiche wave breaking the dam, says Hanisch. Most experts favor the tunnel, which is also Tajikistan's preferred solution, Maskaev says.

As engineers mull ideas for defanging Sarez, scientists are eager to peer inside the megadam. At the September conference, Maskaev proposed taking cores from at least three sites at Usoi. In the late 1980s, engineers were preparing to drill. But the Soviet collapse in 1991 scotched that plan, and newly independent Tajikistan lacked the cash and expertise to carry it out. Both deficits remain. "We're waiting for offers of help," Maskaev says. Some researchers are not sold on the idea. "Drilling would not offer a comprehensive integrated picture of the dam's structure," says Zonn.

One initiative gaining steam is a research campaign. Sassa and colleagues from five countries are planning a detailed look at Usoi next summer, with results ready for a conference in Tajikistan in 2011 to mark the Sarez centennial. By then, says Roschnik, "we should have started working on a long-term solution." If they succeed, Maskaev would be more than happy to wind up the family business—and continue to admire Sarez, for its beauty alone.

–RICHARD STONE

CREDITS (LEFT TO RIGHT): COURTESY OF JÖRG HANISCH; SOURCE: KADAM MASKAEV

MARINE SCIENCES

U.S. Poised To Adopt National Ocean Policy

Faced with more action in the ocean, a new federal council will try to improve planning and resolve conflicts

Stellwagen Bank National Marine Sanctuary shelters a rich array of marine mammals, including the highly endangered North Atlantic right whale. Spanning the mouth of Massachusetts Bay, the sanctuary is also a busy thoroughfare for cargo ships traveling to Boston. For decades, that's been a deadly combination for the whales. But a recent modification to the shipping lanes, which keeps vessels away from the area where right whales are most likely to congregate, has reduced the risk of collision by 56%. And it's made the trip only 15 minutes longer.

Such compromises—this one was worked out by the U.S. Coast Guard, port officials, and sanctuary staff—are relatively rare, however. And the growth of offshore aquaculture, wind farms, and other activities will intensify the competition for ocean space and resources. This week, a White House task force took a significant step toward better planning in federal waters by describing how to balance economic growth with improved protection of federal waters. Its report lays the groundwork for implementing the country's first national ocean policy. "Ocean planning is starting to catch on," says marine ecologist Larry Crowder of Duke University in Durham, North Carolina. "It's nothing less than phenomenal."

There's a pressing need for better planning. States control their waters out to 3 nautical miles; beyond that, some 20 federal agencies have responsibilities for more than 140 laws that apply to federal ocean waters and the Great Lakes. Sometimes those agencies have conflicting missions or don't communicate well. In the course of adjusting the shipping routes through Stellwagen, for example, the sanctuary staff and the Coast Guard learned of a pending request to build two liquefied natural gas (LNG) terminals that would have been dangerously close to the proposed route.

Both a 2003 report from the privately funded Pew Oceans Commission and a 2004 report from the congressionally mandated U.S. Commission on Ocean Policy called for better coordination (*Science*, 23 April 2004, p. 496). "Having an intelligent approach to spatial planning could really fundamentally change the way we do things in the sea," says Elliott Norse of the Marine Conservation Biology Institute in Bellevue, Washington.

Several states are moving toward comprehensive planning in their waters, and Australia has used it to protect the Great Barrier Reef. The national Committee on Ocean Policy created by President George W. Bush fell far short of resolving such inherent conflicts as exist between the Department of Interior, which is in charge of oil and gas leases, and the National Oceanic and Atmospheric Administration (NOAA), which is responsible for fisheries and marine sanctuaries. "Nothing drove the agencies to get out of their bunkers and work toward a common goal," says Christopher Mann of the Pew Charitable Trusts in Washington, D.C.

In June, President Barack Obama asked officials from several agencies to take a fresh look at how to improve the health of the oceans. Their report recommends formation of a National Ocean Council, comprised of senior representatives from 24 federal agencies and co-chaired by the president's science adviser and the head of the Council on Environmental Quality (CEQ). They would provide "high-level policy direction to make sure there's sustained engagement from agencies," says Nancy Sutley, who heads CEQ. Mann is optimistic that this will help reduce conflicts.

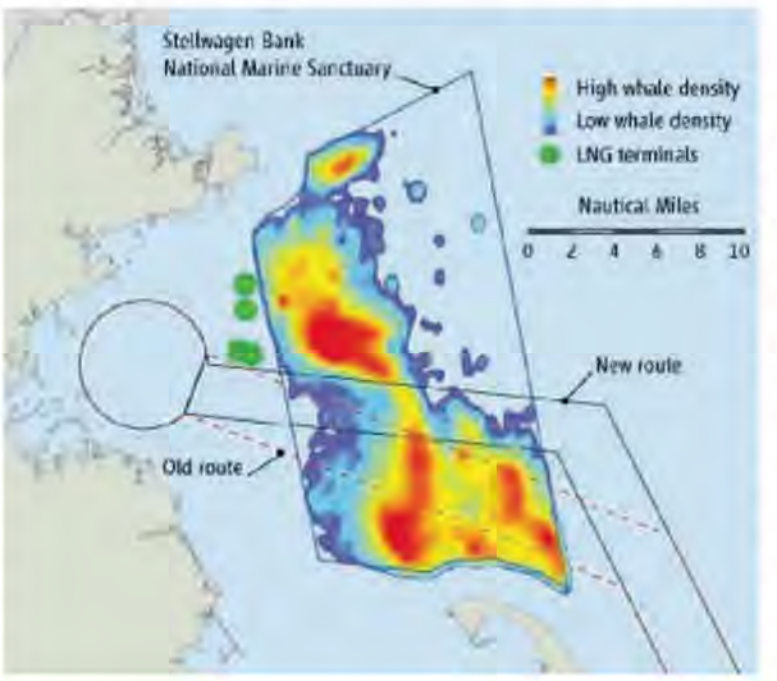
The report also laid out nine priorities for managing the oceans, including focusing on ecosystems, managing for resiliency and climate change, and improving ocean-observing systems. "I was very pleased with the interim report," says Robert Gagosian of the Consortium for Ocean Leadership, an advocacy group in Washington, D.C. "There's so much science in it."

More science will clearly be needed. Regional ecosystem assessments will become a priority, says Gagosian, as will integrating the current patchwork of ocean-observing systems. "The amount of data coming in 24-7 will be tremendous," he says. Even routine survey work on wind resources or bathymetry "could spin off interesting scientific points," adds physical oceanographer David Farmer of the University of Rhode Island, Narragansett. A case in point: The companies building the LNG terminals agreed to install hydrophones to monitor the amount of background sounds and the noise from the terminals. These data could also be used to study how whales are affected.

All the data gathering and analysis will cost money, of course, and major budget increases are unlikely in a tight economy. NOAA Administrator Jane Lubchenco hinted at a Senate hearing last month that she may need to redirect existing resources to meet the new approach. State agencies are in a similar fiscal bind.

But money isn't the first order of business for ocean advocates. Their immediate goal is an executive order, expected by the spring, to create the national ocean policy. Then the new council will spend 6 to 12 months deciding how the planning process should work and how much it might cost.

–ERIK STOKSTAD



Middle way. Adjusting the navigational route into Boston has halved the chances of collisions between ships and whales without impeding commerce.

CREDITS (TOP TO BOTTOM): NOAA; MAP BY MIKE THOMPSON, DAVE WILEY, AND RICHARD MERRICK

CANCER RESEARCH

Melanoma Drug Vindicates Targeted Approach

A mutation-targeted molecular therapy has shown promise against one of the most devastating types of cancer, but how it works is unclear

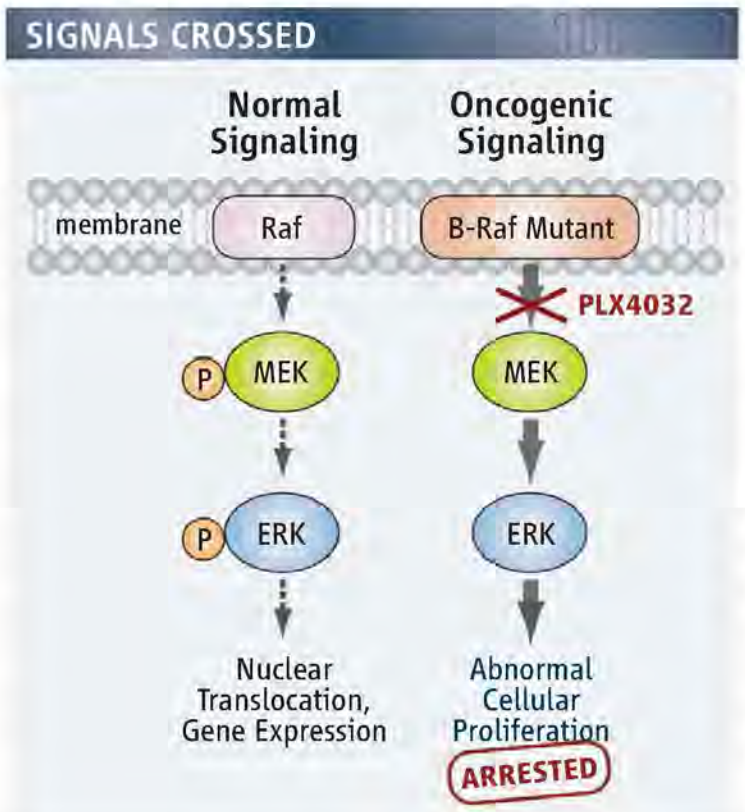
Metastatic melanoma is one of the worst cancers. Average survival time at diagnosis is about 9 months, and many oncologists take a nihilistic attitude toward treatment. "They see patients with metastatic disease, and they say, 'Well, you might as well make out your will; there's really nothing for you,' " says Jeffrey Weber of the Moffitt Cancer Center in Tampa, Florida. The U.S. Food and Drug Administration approved the only metastatic melanoma drug, dacarbazine, in 1975. That drug has a 15% response rate, and all efforts to improve on that rate have failed.

Until this fall, "the skepticism that we would ever be able to break the back of this problem was particularly high," says William Kaelin, a cancer researcher at the Dana-Farber Cancer Institute in Boston. So the 70% response rate reported in September in a phase I trial for a drug from the Berkeley, California, biotech company Plexxikon shocked the field. "It's an astounding leap," says trial principal investigator Keith Flaherty of Massachusetts General Hospital in Boston. "Way out of the ballpark of what … we've ever seen with melanoma therapies in the past." Patient numbers, though, are small, and the compound is not a magic bullet: Patients relapse, on average, after about 9 months, and a survival benefit has yet to be proven. But the Plexxikon compound, PLX4032, is changing the psychological landscape in the melanoma field. Researchers are scrambling to understand why it works in order to design new treatments for other cancers.

PLX4032 is a targeted molecular therapy, one of many now in development. It binds to and inactivates the BRAF protein, which is mutated in about 60% of melanomas. (A single mutation accounts for most of these.) Mutant BRAF turns on signaling in a pathway in cells that controls proliferation, and the drug's efficacy validates the theory that targeting this pathway would destroy tumors. Skepticism had been widespread. "There were many who thought, 'Well, BRAF mutations, who cares?' " says Flaherty. " 'These tumors have so many mutations that there's no one oncogene that's going to be so important.' "

Melanoma trials of other compounds targeting BRAF and a downstream protein, MEK, did not succeed. K. Peter Hirth, the CEO of Plexxikon, says that PLX4032 works because it's "clean": It binds to the mutant form of BRAF much better than it does normal, "wild-type" BRAF. "You really need to have more than 90% pathway inhibition" of BRAF signaling to shut it down, he says. Because it binds preferentially to a target that exists only in tumors, the drug can be given in high doses to patients before serious side effects appear.

PLX4032 is "unlike any targeted therapy anytime in the past," says David Solit, a researcher at the Memorial Sloan-Kettering Cancer Center in New York City. "It seems to be inhibitory of the pathway … only in tumors with the mutation. And that could lead to a change in the way we try to design drugs."



Roadblock. Plexxikon's drug interrupts a key signaling pathway in tumor cells, but not normal cells.

SOURCE: PLEXXIKON

But how the drug works remains unclear. "Why is it so selective for just the mutant?" asks Solit. One possibility is that the drug at high doses binds to wild-type BRAF or other RAF family members in a way that allows the signaling pathway to be active in normal cells instead of shutting it down. For example, a group from the biotech company Genentech presented data at the Molecular Targets and Cancer Therapeutics meeting in November in Boston showing that the same RAF inhibitors that block the pathway in BRAF mutant cells *activate* the pathway in nonmutant cells. Three other research groups have recently reported similar activating activity for RAF inhibitors in normal cells.

That pathway activation in normal cells could explain why side effects don't show up at high doses, speculates Frank McCormick, a cancer researcher at the University of California, San Francisco: "You don't have to worry about side effects of shutting down the pathway."

Pathway activation in normal cells may help, but it could also account for a worrisome side effect. Some PLX4032 patients develop skin lesions known as keratoacanthomas. Researchers suspect the drug might be activating the pathway in skin cells predisposed to growth, hence the tiny lesions. They're benign, but they hint that long-term drug treatment could convert precancerous growths into nonmelanoma cancer.

Regardless of how it works, PLX4032 validates the theory that targeting early "driver" mutations is a feasible way to treat common cancers. "The hope was that by understanding the molecular biology, and in particular identifying the driver mutations, we would make progress," says Kaelin. "This is a very significant step forward."

BRAF mutations are also found in about 10% of colorectal cancers, and less frequently in lung and other cancers—in about 7% of all tumors overall. In theory, PLX4032 should work in all of them. A clinical trial in colorectal cancer is nearly complete.

Whether other cancer mutations can be practically targeted remains to be seen. Cancer genome sequencing efforts suggest that mutations are high in number and low in frequency (*Science*, 5 September 2008, p. 1280). Many drugs might prove necessary for any single tumor type, one for each driver mutation. Kaelin anticipates "drips and drabs of different mutations" in different cancers. "But I'm hoping there are at least a few more of these … highly prevalent mutations waiting to be discovered." And drug resistance is inevitable, as PLX4032 confirms. "It's going to have to be … combinations of two or three drugs that can really effectively kill the tumors," says McCormick. Still, the melanoma results allow researchers to go forward with some confidence. Says Kaelin, "This is a hopeful piece of data that we're on the right track."

–KEN GARBER

Ken Garber is a freelance writer in Ann Arbor, Michigan.

GENOMICS

Ecological Genomics Gets Down to Genes—and Function

The promise of genomics lures ecologists into the once-alien world of molecular biology

KANSAS CITY, MISSOURI—A decade ago, many ecologists and molecular biologists were barely on speaking terms. As universities devoted ever more space and resources to molecular biology, ecologists felt they got the short end of the stick. And those who wanted to incorporate new molecular techniques into their studies were hamstrung by grants too small to pay for the new technologies.

But in recent years, ecologists and molecular biologists have been finding common ground—to the benefit of both disciplines. "Ecology needs better grounding in mechanisms, particularly molecular mechanisms. And those [researchers] who focus on the molecular level often do so at the expense of reality," says Jack Schultz, an ecologist at the University of Missouri, Columbia. "These two areas really need each other." Now, says Schultz, "when you walk around, you see people [doing] genomic studies on all kinds of organisms."

Some of the results of this detente were on display last month, when about 90 researchers and students gathered* to discuss progress in ecological genomics—the application of genomic techniques and resources to the study of ecology. Some are applying tools such as microarrays or RNA interference to their favorite study animal or plant. Others are developing genetic maps and databases of gene fragments for nonmodel organisms, with the goal of eventually sequencing those genomes. These efforts are pinpointing genes involved in ecologically relevant traits, and researchers are beginning to figure out the roles those genes play in an organism's function and evolution. "It's not enough to identify a list of candidate genes for adaptation; you now need to integrate a functional approach," says Jay Storz, an evolutionary biologist at the University of Nebraska, Lincoln.

*The Ecological Genomics Symposium was held 13 to 15 November in Kansas City, Missouri.

Food safety. Honey bees usually don't eat raw nectar but convert it into honey.

How bees are like us

May Berenbaum, an entomologist at the University of Illinois, Urbana-Champaign, has long been interested in innovations in the arms race between insect herbivores and their hosts. Her work has focused on genes for cytochrome P450, a family of enzymes that break down toxins. (One particular P450 enables a black swallowtail caterpillar, for example, to feast on the normally toxic wild parsnip and its relatives.) For many years, Berenbaum tracked down P450 genes one at a time, but now that several genomes have been sequenced, she can use computer programs to search for typical P450 sequences across an organism's entire genome and verify them with more detailed studies. More than 7000 P450 genes are now listed in public databases; insects generally have scores of them, and some plants have hundreds.

As she described at the meeting, Berenbaum noticed something strange when she looked over the P450 counts for the honey bee, mosquito, fruit fly, and red flour beetle genomes. Honey bees had a mere 48, compared with 87 in the fruit fly, 112 in the mosquito, and 144 in the beetle. "How could they function with so few [toxin] metabolism genes?" she wondered.

She ruled out the possibility that the small number was attributable to the fact that female worker bees have just one set of chromosomes instead of the usual two: *Nasonia vitripennis*, a small parasitoid wasp, has the same unusual genetic system, yet it has 90 different P450 genes. Berenbaum next tried activating the honey bee's detoxification genes by exposing the insects to a chemical that usually triggers P450 gene activity. She got no response. It was as if honey bees didn't often encounter toxins.

At first this finding didn't make sense. Honey bees gather nectar from a wide range of plants, and nectar contains a variety of toxins, so Berenbaum expected that the bees would have a robust, readily activated detoxification program. But as she thought about it more, Berenbaum hit on a possible explanation: Honey bees rarely eat "raw" food. Instead, they collect nectar and pollen and process it into honey and bee bread in the hive. Sitting in the warm hive, nectar's toxins break down, nectar is dewatered, and its sugar profile and pH change as it is transformed into honey. The transformation likely renders the food less harmful. The honey bee "is the only other organism [besides humans] that prepares its food," says Berenbaum. "They use social behavior, as do we, to deal with toxic foods."

The work "is an exciting example of genome-enabled research—particularly the poten-

Go light. In White Sands, New Mexico (*above*), mutations have lightened the eastern fence lizard (*right*, *top*) and little striped whiptail lizard (*far right*, *top*) to help them blend in better.

CREDITS (TOP TO BOTTOM): JOSEPH SPENCER; PROVIDED BY ERICA BREE ROSENBLUM; (INSETS) E. B. ROSENBLUM ET AL., *AMERICAN NATURALIST* 167 (JANUARY 2006) © THE UNIVERSITY OF CHICAGO PRESS

tial for comparisons between genomes of different species that have different lifestyles," says Erica Bree Rosenblum, an evolutionary biologist at the University of Idaho, Moscow.

How deer mice live the high life

Several talks at the meeting indicated how evolutionary biologists are coming to depend on genome sequence data to provide important insights into the evolution of specific traits. "Genomic technology [has] provided us with the means of identifying the genetic basis of adaptation and speciation," says Storz. "The future lies in obtaining a more mechanistic understanding of those processes."

Storz's group has already begun to go down that path. They have characterized changes in genes for hemoglobin—a component of blood that transports oxygen—that enable deer mice, *Peromyscus maniculatus*, to thrive at oxygen-poor high altitudes. A survey of the sequenced genomes of the lab mouse, human, and lab rat revealed that the organization of the hemoglobin genes was conserved and "showed where in the genome these genes were located," says Storz. Two copies of the gene for the alpha globin subunit appeared together in one location; two copies of the beta globin subunit appeared together in another spot. He used the sequences and their locations to track down those same genes in the deer mouse.

At the meeting, Storz and his colleagues described how hemoglobin genes were quite different in mice living at high altitudes compared with those at low altitudes. These genes were more different than were other genes from the two locations, indicating that they experienced selection pressures in high- and low-altitude environments that other genes did not.

Based on the sequences of these subunit genes, Storz and his colleagues pinpointed five amino acid changes in the alpha globin subunits and four in the beta globin subunits associated with altitude. They purified hemoglobin from deer mice of known genetic makeups and tested how well each version of hemoglobin grabbed onto oxygen. The versions from mice living on the peaks had high oxygen affinity—which made taking in oxygen in the rarefied mountain air more efficient. Now Storz and his colleagues are making artificial hemoglobins with different combinations of the changes they see in the high-altitude mice to see which changes are most important.

"What [Storz] is doing is really at the cutting edge, the foreground, of ecological, evolutionary and functional genomics," says Theodore Morgan, an evolutionary biologist at Kansas State University in Manhattan. "He's able to link not only the genotype with the phenotype, but he's also able to establish a mechanistic link [in] how the different alleles of hemoglobin are changing between the high altitudes and low altitudes."

Mountain high. Researchers studying high-altitude deer mice (*above*) find special hemoglobin genes help these mice breathe easy.

CREDITS: UNIVERSITY OF NEBRASKA; (INSET) © MARK A. CHAPPELL

How lizards lighten their skin

Rosenblum has also used genomics to probe mechanisms that underlie the adaptations organisms make to their environment. Her animals of choice are three species of lizard in White Sands, New Mexico—a large patch of white gypsum surrounded by dark desert scrub. Over the past 10 years, Rosenblum and her colleagues have determined that the three species have different mutations of the *Mc1r* pigment gene that cause normally brown skin to be quite pale. When mutated, *Mc1r* causes less brown pigment to be produced, helping the lizards blend in with the white sand.

She was puzzled that the mutations have different effects in two of the lizards. In the eastern fence lizard (*Sceloporus undulatus*), the blanched color was passed on as a dominant trait, whereas in the little striped whiptail lizard (*Aspidoscelis inornata*), it was a recessive trait. This difference probably affected how quickly the mutation spread in the White Sands populations of each species. When she tested the effect of each mutation on the function of the Mc1r protein in cell cultures, she discovered that the fence lizard's defective protein does not integrate well into the cell membrane, where it normally sits. The whiptail lizard's defective protein settles into the membrane just fine, however, but it doesn't pass signals along very well. "Even though we have the same gene, we have different [ways] the function is compromised," she reported at the meeting.

The lightened skin also changes other skin-color patterns—in particular, the yellow, orange, blue, and green that lizards rely on for social cues. So Rosenblum wondered how these changes have affected courtship and territorial behavior. She and her colleagues tested whether White Sands males react differently to each other compared with males from the surrounding desert. They also looked at the White Sands males' preferences for females of like or different color. White males were more aggressive toward other white males and more attentive to the white females, Rosenblum found: "The lizards, in a couple of thousand generations, can tell the difference." But the color changes also had an unexpected effect: White males tended to court the desert scrub males—most likely because the desert scrub males' blue belly patches were about the same size as the White Sands females' belly patches, which made them look like White Sands females. "We have a link between natural and sexual selection," she adds. "Therefore, a single mutation can have important effects for both adaptation and the early stages of speciation."

As the work with lizards, deer mice, and honey bees shows, ecologists have converged on genomics from very different perspectives. Yet once genomics has helped them find specific genes and identify selective pressures, their interests broaden to include physiology, cell biology, and interactions with the environment. As Michael Herman of Kansas State University points out, those in this field "are spanning all levels of biological organization." **–ELIZABETH PENNISI**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Since 1848, AAAS has served as a prominent voice to advance science and as a valuable resource for scientists, educators, and policy makers. For the past 100 years, part of this mission has included publishing the journal *Science*, one of the world's premier peer-reviewed research journals. Working together to disseminate the most compelling discoveries across all scientific disciplines, AAAS and *Science* continue to fulfill their mission of advancing science for the benefit of all.

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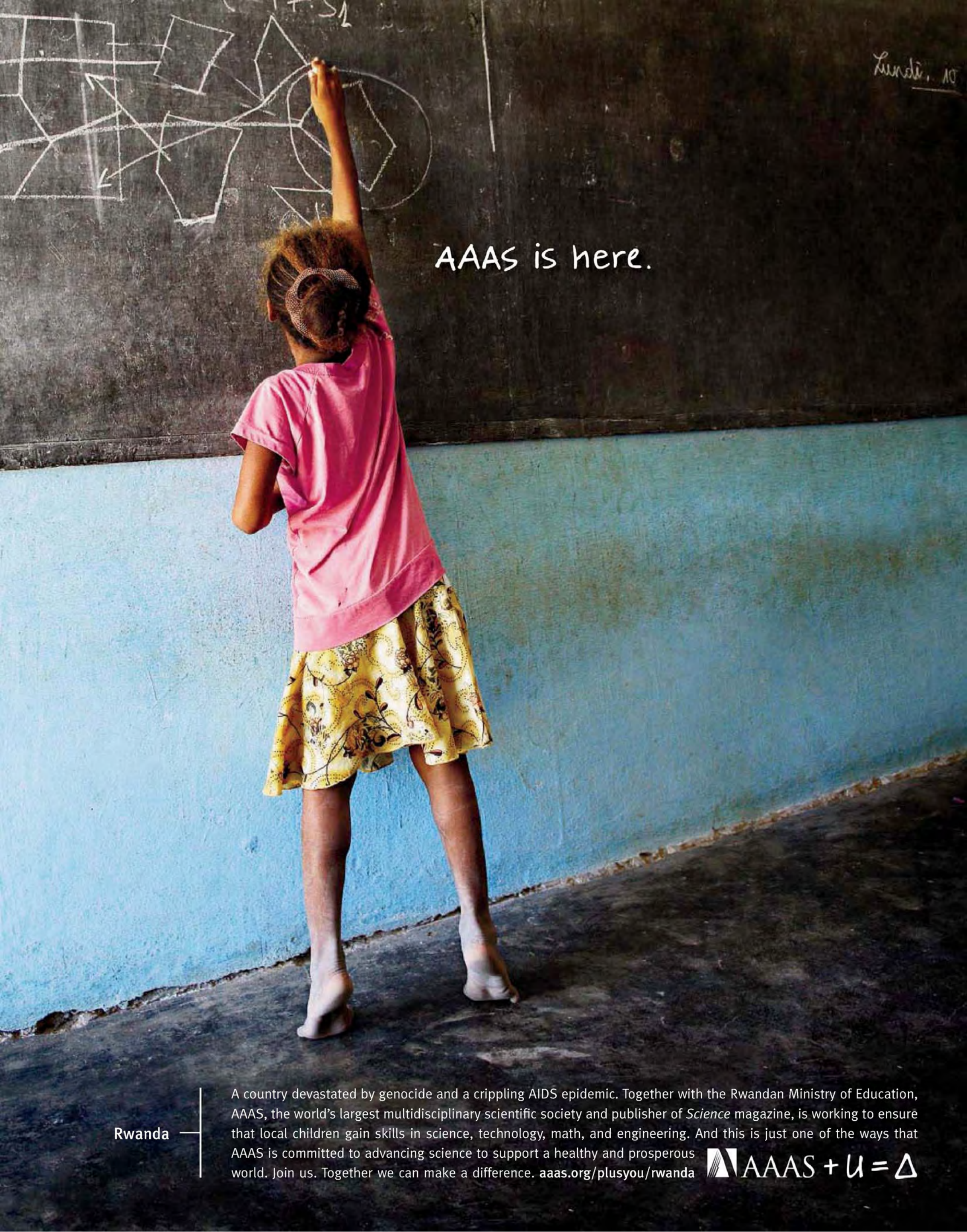

Rwanda

A country devastated by genocide and a crippling AIDS epidemic. Together with the Rwandan Ministry of Education, AAAS, the world's largest multidisciplinary scientific society and publisher of *Science* magazine, is working to ensure that local children gain skills in science, technology, math, and engineering. And this is just one of the ways that AAAS is committed to advancing science to support a healthy and prosperous world. Join us. Together we can make a difference. **aaas.org/plusyou/rwanda**

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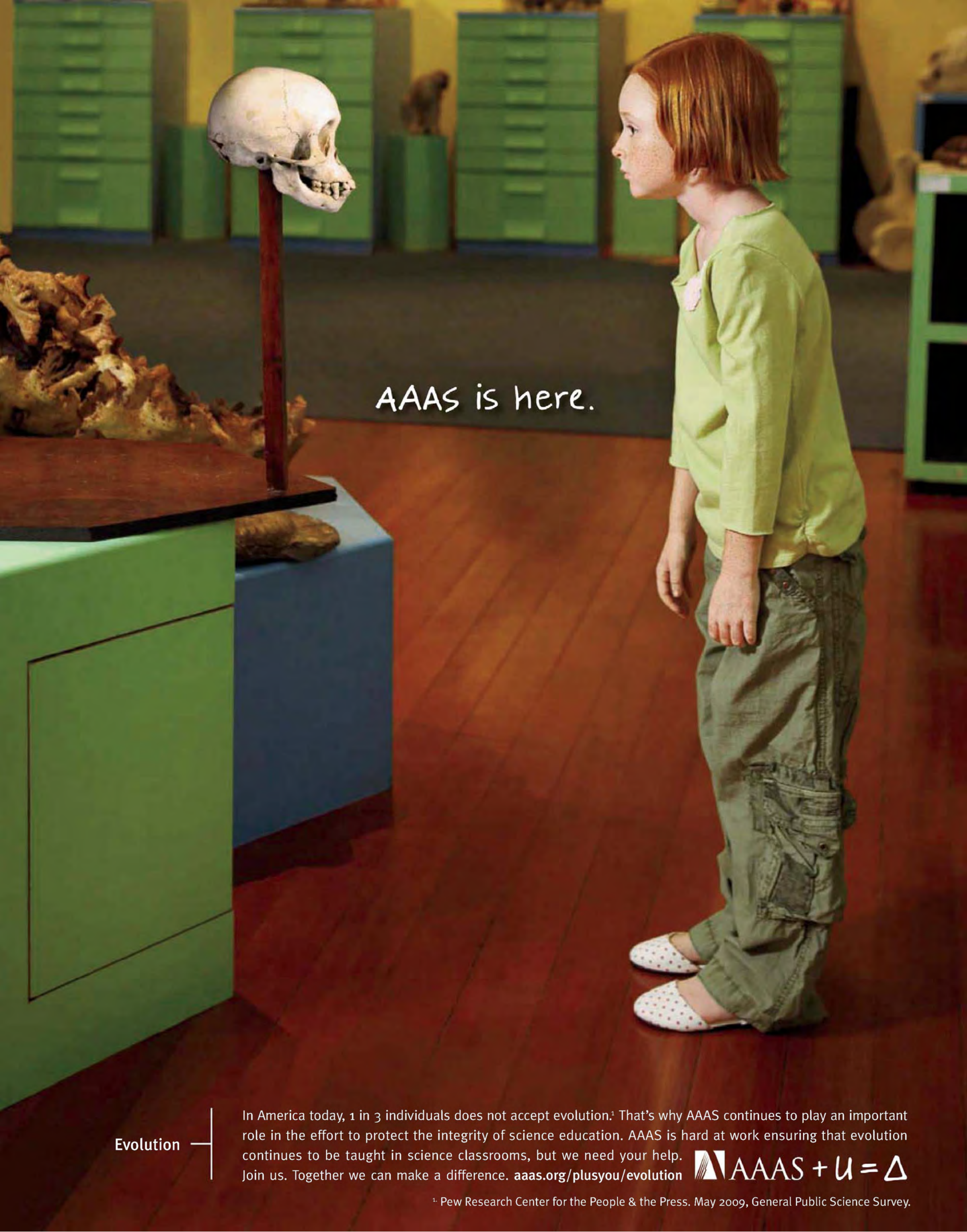

Evolution

In America today, 1 in 3 individuals does not accept evolution.[1] That's why AAAS continues to play an important role in the effort to protect the integrity of science education. AAAS is hard at work ensuring that evolution continues to be taught in science classrooms, but we need your help. Join us. Together we can make a difference. **aaas.org/plusyou/evolution**

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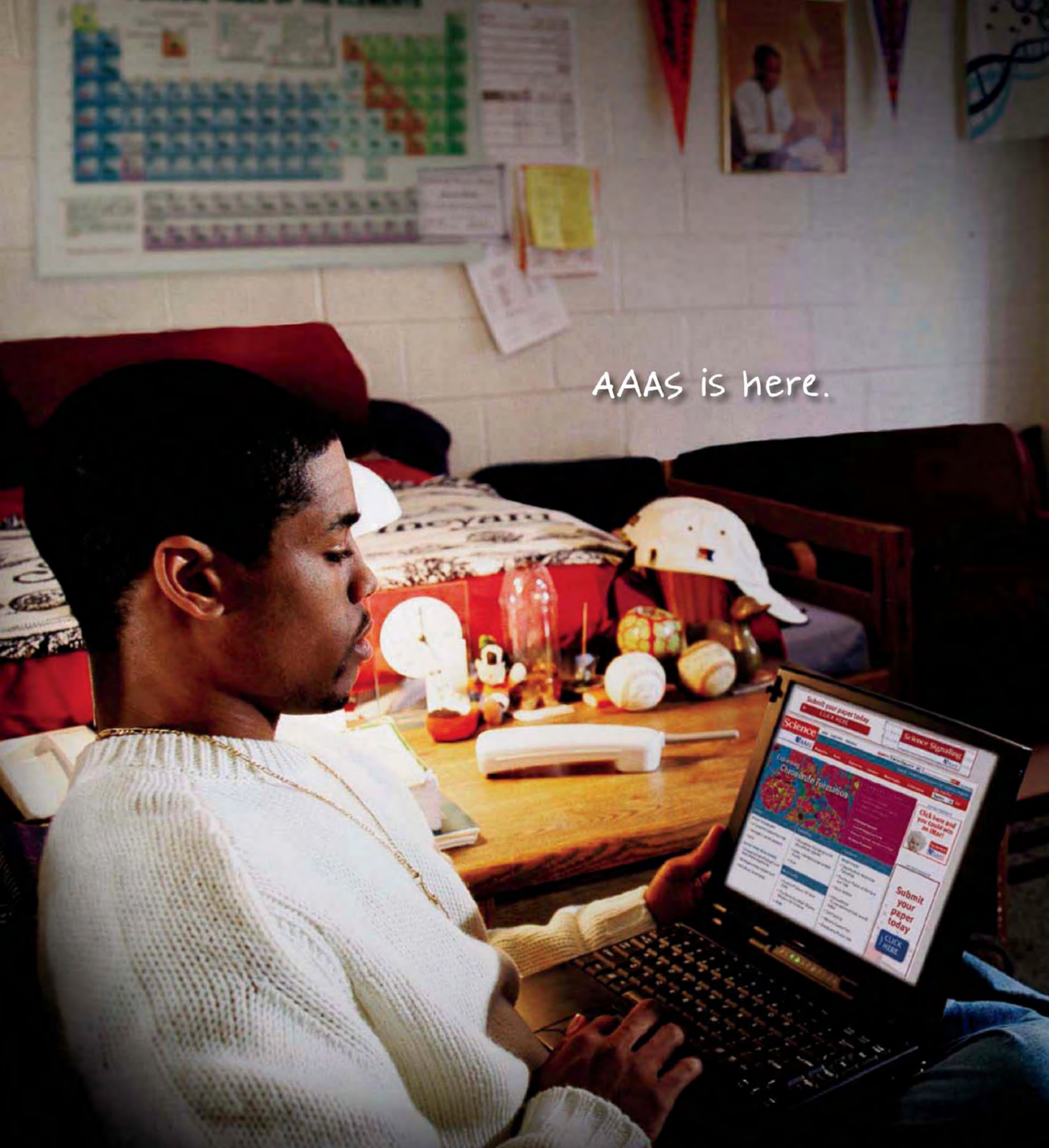
[1] Pew Research Center for the People & the Press. May 2009, General Public Science Survey.



HBCU-UP National Research Conference

Historically Black Colleges and Universities (HBCUs) increase the number of underrepresented ethnic minorities qualified for education and research in science, technology, engineering, and mathematics (STEM). AAAS partners with NSF to host a national gathering that highlights undergraduate student research to enhance the quality of STEM education. And this is just one of the ways that AAAS is committed to advancing science to support a healthy and prosperous world. Join us. Together we can make a difference. **aaas.org/plusyou/hbcuup**

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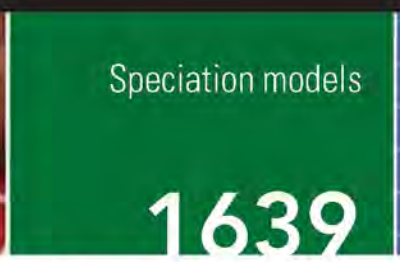

LETTERS

edited by Jennifer Sills

Time for DNA Disclosure

THE LEGISLATION THAT ESTABLISHED THE U.S. NATIONAL DNA INDEX SYSTEM (NDIS) IN 1994 explicitly anticipated that database records would be available for purposes of research and quality control "if personally identifiable information is removed" [42 U.S.C. Sec 14132(b)(3)(D)]. However, the Federal Bureau of Investigation (FBI), which controls the database, has published no research derived from NDIS and has declined to disclose these records to academic scholars. The National Research Council recently noted that "methods developed in crime laboratories to aid in law enforcement" would benefit from the contributions of academic scientists (*1*). We believe the time has come for the FBI to release anonymized NDIS profiles to academic scientists for research that will benefit criminal justice.

Disclosure of NDIS profiles would allow independent scientists to evaluate some of the population genetic assumptions underlying DNA testing using a database large enough to allow more sensitive evaluation of population structure. The publicly available population databases used to date for statistical estimation of the frequency of DNA profiles are relatively small ($N \approx 1000$), consisting of convenience samples analyzed over a decade ago (*2*, *3*). In contrast, NDIS has grown to over 7 million complete 13-locus short tandem repeat (STR) genotypes (*4*). Analysis of these data would allow more powerful tests of independence within and between loci, as well as assessment of the efficacy of the theta factors used to compensate for population substructure. (To the extent the data are identified by state, analysis of NDIS data could also yield important information about the most appropriate geographic scaling for allele frequency estimates.)

CREDIT: ANDREI TCHERNOV/ISTOCKPHOTO.COM

The large sample size also allows real-world tests of propositions that previously have been addressed only by simulation. For example, it would allow tests of the frequency with which three-person mixtures could produce profiles consistent with two contributors (*5*); kinship analysis could allow assessment of how match probabilities are affected by the number of close relatives in the database (*6*, *7*); and multivariate analysis could be used to evaluate the extent to which DNA profiles cluster due to identity by descent. As studies of smaller databases have shown, researchers need not know a priori the precise number of relatives in the database, nor their ethnic/racial background, to perform these assessments (*6*, *8*). Indeed, scholars who have examined smaller databases have called for examination of national databases (*6*, *8*, *9*). Access to the anonymized 13-locus genotypes would allow more powerful analyses of these important issues than was previously possible.

Analysis of NDIS can also yield valuable insights into the frequency and circumstances under which certain typing errors may occur. A review of a government database from Victoria, Australia, containing 15,021 9-locus STR profiles shows how important such a review can be for "quality control purposes" (*10*, *11*). The study found an error rate of about 1 in 300 for the typing of reference samples, which raises concerns about missed opportunities to develop investigative leads.

Disclosure of NDIS profiles would not violate any meaningful privacy interests (*12*). (There are easier ways to determine whether an individual has a criminal record than searching such a database, and the profiles would not be useful for medical diagnoses.) The profiles in the Victoria, Australia, database have been widely circulated for years with no known harm occurring. The U.S. government regularly argues to courts that broad mandatory DNA collection statutes are not unconstitutional precisely because the 13 genetic loci are noncoding and thus have no power to reveal any sensitive information. Moreover, as most research scientists know well, the government frequently releases sensitive information under controlled conditions to verified researchers. Even within the criminal justice context, law enforcement officials have made available data about the age, race, gender, geographic residence, and a wide range of other information about criminal offenders so that researchers can conduct studies aimed at improving and enhancing effective law enforcement.

Some have suggested that the release of NDIS profiles would be unduly burdensome (*13*), but the relevant fields in the SQL database could be copied in a matter of minutes.

Open access to data is a fundamental tenet of science. The need for openness was reinforced by the recent National Research Council report, which decried the insularity of forensic science and called for greater involvement of the academic community in assessment, validation, and improvement of forensic science methods (*1*). Law enforcement should honor the norms of science and open the NDIS and other government DNA databases to independent scientific scrutiny. Doing so poses no meaningful risk and can only strengthen the quality of forensic DNA analysis.

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Weighing Reward and Punishment

IN THEIR REPORT "POSITIVE INTERACTIONS promote public cooperation" (4 September, p. 1272), D. G. Rand *et al.* find that targeted reward is at least as effective as targeted punishment in maintaining cooperation. In their experiment, infrequent reward may be sufficient because the group is small and interacts repeatedly. However, in real-world situations, punishment may be the more effective and cost-efficient option.

In many real-world cases, unlike Rand *et al.*'s example, the cost to Player A of giving Player B a material reward is roughly the same as the benefit Player B receives from the reward. (The benefit of nonpecuniary rewards, such as praise, may exceed their cost considerably. Rand *et al.* suggest this, but their experiment is not set up to provide evidence.) Thus, the cost of cooperation is simply shifted to those who provide the reward. However, the threat of punishment provides a less costly lever to force cooperation, even when the threat must be carried out. The cost of a match and a gallon of gasoline is much less than cost to repair the damage they could cause. Likewise, nasty words can hurt much more than the effort it takes to say them.

In real-world situations, when people are not interacting in a small group and when they are motivated by money, the threat of punishment is effective. Laws are based largely on this insight.

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Response

BARON ARGUES THAT INFREQUENT PUNISHments are more cost efficient than infrequent rewards. But our experiment does not represent a situation of intermittent rewarding. Instead, we have shown that contributions to the public good can be maintained by linking the public goods game to cooperative, wealth-producing pairwise interactions. Low contributors are denied cooperation in pairwise interactions, while high contributors are rewarded. Due to the ubiquity of such opportunities for targeted interaction, there is no need for costly peer punishment to enforce cooperation. Full cooperation in both the public and pairwise interactions leads to the best possible payoff. Thus, adding punishment cannot result in better outcomes.

Baron challenges the real-world applicability of the non–zero-sum rewards in our study. However, the availability of wealth-generating, non–zero-sum interactions is the essence of all social dilemmas—including the Prisoners' Dilemma (*1*–*5*), of which our reward interaction is an example, as well as the Public Goods Game (*6*–*9*) itself. These games represent the multitude of different

cooperative interactions in which two or more people working together can achieve more than each person could alone. For example, consider mutually beneficial trade: Both parties pay the cost of abandoning something worth less to them than to the other, in order to gain something they find relatively more valuable. To enforce public cooperation, one can refuse to trade with those who do not contribute to the public good. Baron's claim that life offers few opportunities to create material benefits for others through cooperation questions the relevance of all work on social dilemmas, including his own (*10*).

Baron concludes by mentioning the role of punishment in law. However, our paper and most others on costly punishment (*4*, *5*, *7*–*9*) investigate peer punishment, not institutionalized punishment. The latter deserves further empirical and theoretical exploration.

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CORRECTIONS AND CLARIFICATIONS

Editors' Choice: "Microbial influences" (4 December, p. 1321). The image accompanying the text should have been credited to Ivanov *et al.*, not Gaboriau-Routhiau *et al.*

Books *et al.*: "Science goes Hollywood" by C. Bohannon *et al.* (4 December, p. 1348). The first sentence of the reviewers' affiliations was inadvertently dropped. The reviewers are members of NeuWrite, a nonfiction writing group at Columbia University (www.neuwrite.org).

Policy Forum: "Bridging the Montreal-Kyoto gap" by J. Cohen *et al.* (13 November, p. 940). The author's e-mail should be jcohen@eosclimate.com. The HTML online version has been corrected.

Reports: "Engineering entropy-driven reactions and networks catalyzed by DNA" by D. Y. Zhang *et al.* (16 November 2007, p. 1121). In Fig. 4B, domain $\overline{4a}$ should have been domain $\overline{4t}$, with a length of 7 nucleotides. The corrected figure appears below. The following text should also be added to the Fig. 4B caption: "Domain $\overline{4t}$ has identity 5′-TTGAATG-3′ and is a subsequence of domain $\overline{4a}$."

ECONOMICS

Rich Financial Lives of Poor People

Anirudh Krishna

Far from being disconnected from the market economy, poor households, including those living on less than one dollar a day, are deeply invested in financial transactions. Because these transactions are mostly informal, thus undocumented, they remain invisible to one-time visitors and others who look at written records. But if one were to take the trouble of visiting households twice a month over the course of a year, recording the details of all financial transactions, then one would recognize how diligently poor people, using a variety of instruments, manage their portfolios. Conducting such an exercise for 300 households in Bangladesh, India, and South Africa, the authors of *Portfolios of the Poor* found that a "triple whammy" characterizes the financial lives of the poor. Incomes are not only low; they are also irregular and unpredictable. Large expenditures arise suddenly on account of illnesses, deaths, insect infestations, and demolition drives. Inflows and outflows of money can be, and quite often are, severely mismatched over time.

Yet, as the authors document, only very blunt tools are available for smoothing cash flows. All poor households set aside money in savings, but they tend to store these savings in unproductive and insecure forms: "Mumtaz in a locked box in a drawer in the cupboard, Subir in a cloth bag tied into the roof timbers." Short-term consumption loans, necessitated by force of circumstance, are most often taken out from relatives and friends and, if need be, from informal moneylenders, who charge high interest rates.

With the help of a series of life stories, the authors show how informal arrangements have the advantages of convenience and flexibility. No forms of application need be filled out; no "stone-faced tellers" need be confronted. Money required for emergency medical expenses can be immediately obtained, and it can be returned in small, irregular installments, as and when it is earned. Informal lenders understand the conditions in which poor people live; they are often quite poor themselves.

But informality has the disadvantages of unreliability and lack of depth. One can never be sure that the amounts required will be forthcoming when necessary. Certainly, large amounts are hard to procure using these means. Further, there is a lack of privacy. One South African interviewee informs the authors that "The owner gives [a loan] to you easily, but then he also embarrasses you when he asks you in front of everyone when you are going to pay." On the other hand, the formal banking system has little to offer people who lack collateral and whose frequent small transactions can impose unbearably high overhead costs. Thus, resorting to informality is hardly always an act of choice.

The authors' account suggests much that can be done to ease the financial conditions of poor people. Simultaneously, businesses can earn more revenues. The trick lies in matching the flexibility and convenience of informality with the reliability and depth of formal credit institutions.

Seeking to fill this niche, microcredit operations have proliferated across the world. The authors examine many of them, both formal and informal. Not all have absorbed the right lessons about the financial lives of poorer people. Some microlenders cater to a narrow range of needs, for instance, advancing money only for business or productive purposes (but not for emergencies or other consumption requirements). Nimbler operators, such as the Grameen Bank (which the authors discuss in considerable detail), have realized that money is a fungible commodity: It will be used willy-nilly for serving a variety of needs, not all of which may be connected with the stated purpose of the loan. If a sick child is in need of immediate medical attention, money borrowed with the intent of purchasing stock-in-trade will be used instead for paying doctors' fees.

Portfolios of the Poor
How the World's Poor Live on $2 a Day

by Daryl Collins, Jonathan Morduch, Stuart Rutherford, and Orlanda Ruthven

Princeton University Press, Princeton, NJ, 2009. 295 pp. $29.95, £20.95. ISBN 9780691141480.

Analyzing these examples, the authors conclude that a newer and better way of doing business involves a more flexible and personalized pattern of micro-lending: Give borrowers the "chance to make small-scale savings of any value at any time with the right to withdraw on demand" and offer loans of different sizes "that can be taken quickly… and repaid in small (and, if necessary, irregular) installments."

In one of his early writings, Muhammad Yunus (Bangladeshi economist, founder of the Grameen Bank, and later a Nobel Peace Prize winner) observed, "Every human being has enormous capacity, enormous potential. Many people never get a chance to discover what capacity they have and how far they can go. This is not the fault of the poor person…. The fault lies instead with the societal arrangements that we have made, with the institutional designs we have introduced" (*1*). The book's human stories help illustrate this proposition.

Poor people's economic conditions are held in check by a variety of positive and negative influences. We need diverse insti-

Crucial cash. A Bangladeshi woman holds reimbursement money for a Grameen Bank loan.

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tutions that can better enable poor people to cope with these effects, helping amplify the effects of positive forces while reducing or nullifying the effects of negative ones. Better health care systems are essential for preventing further impoverishment, but better means of financing health care are also necessary. Although customary expenses on funerals and weddings must be reduced, until that is achieved appropriate means of financing have to be found. Droughts and floods will continue to impose sudden and heavy costs, more so now on account of climate change. The resulting human misery will be mitigated to a considerable extent if caring institutions providing flexible loans are at hand.

As *Portfolios of the Poor* demonstrates, poor people lead rich and complex financial lives. More than anyone else, they marshal money flows with care. Financial institutions and instruments tailored for their particular conditions will give them a fighting chance for beating the odds.

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BROWSINGS

Logicomix: An Epic Search for Truth. Apostolos Doxiadis and Christos H. Papadimitriou; art by Alecos Papadatos and Annie Di Donna. Bloomsbury, New York, 2009. Paper, 347 pp. $22.95. ISBN 9781596914520. London. £16.99. ISBN 9780747597209.

This graphic novel spins an entertaining yarn from the 19th- and early-20th-century debates on the nature of mathematical truth. At the outbreak of World War II, philosopher Bertrand Russell recounts his quest to answer the question "what is logic?" His summaries of contributions from mathematicians and logicians such as Alfred North Whitehead, Gottlob Frege, Georg Cantor, David Hilbert, Ludwig Wittgenstein, and Kurt Gödel (below) are mixed with memories of his lonely youth, fears of hereditary madness, and amatory adventures. Doxiadis and his collaborators pop up in interludes throughout the book—discussing plot and development, strolling the streets of Athens, and, lastly, reflecting on a performance of Aeschylus's *Oresteia.* At the book's end, they reveal some of their departures from reality and offer additional details about characters and ideas.

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BIOLOGICAL WEAPONS

We Need to Talk About Bioweapons

Brian Balmer

Biologists should not stand on the sidelines of debates about biological weapons and how to control them. It is an ugly subject, but one that demands attention from the life sciences community. Yet research cited in Lynn Klotz and Edward Sylvester's *Breeding Bio Insecurity* suggests that most life scientists are reluctant to engage with this taboo issue. Nor do they wish to contemplate that their work might fall into the category of "dual-use," work pursued with beneficial intent but which could also be put to malign use. If biologists fail to speak out about how to control the less-desirable implications of their endeavors to produce beneficial knowledge, then someone else will speak not simply instead of them but on their behalf.

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That it is possible to steal science's collective voice in this way was made real to me on a visit to the United States a few years ago. I heard an official from the Department of Homeland Security claim that patriotism was the prime motivation for the large number of scientists he saw applying for the, then, new and massive injection of funds into biodefense research. It was not his claim as such that troubled me. Undoubtedly, even in the competitive world of scarce grant funding, patriotism might well be one among many motives for scientists to chase after biodefense money, despite its attendant pull on the research agenda toward work on the most dangerous pathogens. A more fundamental concern was that here was someone speaking as if he was the sole representative of the scientific community, with the implication that this community endorsed, by its actions, a claim that the massive injection of funds was commensurate with the nature and level of threat of a bioweapons attack.

But then, how to agree or disagree with this claim? Biological warfare is a swamp of secrecy and uncertainty in which it is hard to find any stable ground. One helpful guide is Gregory Koblentz's well-researched and measured-toned *Living Weapons: Biological Warfare and International Security*. While Koblentz (a political scientist with the biodefense program at George Mason University) is in no doubt that we should be concerned about biological weapons, he is keen to provide a sober assessment of the topic. He focuses on how we act to prevent the misuse of life sciences in state-operated programs and, to a lesser extent, how we try to avoid bioterrorism by substate groups. Success, he repeatedly points out, is no easy task. Biotechnology is dual-use or, in Koblentz's terminology, multiuse. Botulinum toxin, as he notes, is a potential weapon, but it also can

be used as the cosmetic wrinkle treatment Botox or to help treat muscle spasms. Even within the confines of military research, the line between offensive and defensive studies is blurred. Whether the aim is to develop a vaccine or a weapon, it is necessary to produce live pathogens (and maintain them until they are killed, attenuated, or weaponized, depending on their final use). Added to this mix of complications are endemic secrecy and the fact that, from a distance at least, there is little to distinguish between a pharmaceutical facility and a pathogen plant.

Living Weapons
Biological Warfare and International Security

by Gregory D. Koblentz

Cornell University Press, Ithaca, NY, 2009. 273 pp. $35, £23.95. ISBN 9780801447686.

Breeding Bio Insecurity
How U.S. Biodefense Is Exporting Fear, Globalizing Risk, and Making Us All Less Secure

by Lynn C. Klotz and Edward J. Sylvester

University of Chicago Press, Chicago, 2009. 268 pp. $27.50, £19. ISBN 9780226444055.

Koblentz provides clear illustrations of how these problems play out in practice. Using the example of the United Nations Special Commision biological weapons inspections in Iraq after the first Gulf War, he provides readers with a vivid sense of the enormous task that faced inspectors as they struggled to piece together the evidence. One thing is clear: the facts here did not speak for themselves. Even when faced with the same evidence, inspectors diverged in opinion. A telling example is the plant at Al Hakam: Whereas one inspection team reported "absolutely no evidence of participation in a biological weapons program," another claimed the plant was "highly suspicious." In the end, vital information was supplied by the 1995 defection of Saddam Hussein's cousin (a senior figure with direct knowledge of Iraq's biological warfare program). In a later chapter, Koblentz returns to this often-crucial role that defectors and other intelligence sources play in bioweapons control. He examines U.S. surveillance of the Soviet Union's Cold War biological warfare program as well as U.S. intelligence prior to the 2003 Iraq invasion. Noting, again, how facts require interpretation, he points out the wider assumptions and pressures that influenced the intelligence community's assessments of the adversary's capabilities. An additional point, not dwelt on by Koblentz, is the assumption shared by intelligence, political, and military authorities that "the adversary" is a homogeneous unit that possesses complete knowledge of its own capabilities. Contrary to this idea—and as Koblentz describes—in the former Soviet Union the military repeatedly misled the Kremlin on the activities of its bioweaponeers, which suggests a far more fractured picture of who knew what, where.

Fracturing of this kind is enabled through secrecy, a pervasive feature of biological weapons programs that Koblentz explores lucidly through case studies of the former Soviet Union and South Africa. He concludes that secrecy has corrosive effects, providing a shield from wider civilian oversight. Sometimes, ironically, these corrosive effects are desirable, insofar as they facilitate the self-destruction of a program. In the South African case, Koblentz details how secrecy, rather than shielding the creation of dangerous weapons, allowed corruption to set in as senior scientists diverted significant funds into purchasing real estate and funding lavish vacations. Although not good, such misappropriation was certainly the better of two evils.

Secrets are also central to Klotz and Sylvester's *Breeding Bio Insecurity*, in which the focus is on the United States. This contrasts with Koblentz's analysis, which could be faulted for a concentration on "distant" states (Iraq, South Africa, and the former Soviet Union) that inadvertently diverts readers' attention from the history of bioweapons programs in countries such as the United States, the United Kingdom, and Canada. Klotz (at the Center for Arms Control and Non-Proliferation in Washington, DC) and Sylvester (a science journalist) spotlight the huge sums of money invested by the U.S. government in biodefense research. Here, they claim, secrecy is having corrosive effects. They also argue that the money pouring into biodefense research is out of proportion to the level of threat. In addition, they contend, this massive investment has backfired to create more risk because now more scientists are working with dangerous pathogens, thus increasing the chances of accident, theft, and deliberate misuse. Not, they stress, that all work on biodefense should be terminated. Instead, the authors call for balance in circumstances that currently veer from lack of oversight and transparency to the restrictive extreme where the "select agent" list of dangerous pathogens requires scientists to navigate a maze of bureaucracy before, during, and after carrying out any research on these organisms. As Klotz and Sylvester summarize their position, "We need to enforce reasonable regulations to protect the public, and we need to protect and not impede scientists in their vital work."

Their argument deserves serious attention. So do not be deterred by their rather histrionic opening chapter, with its talk of unleashing dreaded pandemics, "charging down this dangerous path out of contradictory motivations that can only be self-defeating," and bioweapon attacks striking "like a hurricane … sweeping in with predictable malevolence but unimaginable force." By the time I got to being informed that the contents of a high-containment biodefense laboratory was coming to my neighborhood soon, I half expected to see at least one of the four horsemen of the apocalypse gallop off the page. This, of course, may be the fault of the publisher wanting to appeal to the mythical "educated layperson." (Along these lines, I recall colleagues working on a serious book in this field earnestly being asked by their publisher to call it *The Devil in the Freezer*.) So just skip to the second chapter, where—although still in a campaigning and strident mood—the authors settle down, attend to the evidence, and marshal ammunition for their argument. And here they do themselves justice, having consulted numerous documents written by, and conducted interviews with, several experts on biological weapons control and public health.

A further strength of *Breeding Bio Insecurity* is that it ends with a refreshing look at what might be done under the Obama administration. Klotz and Sylvester advocate, for example, the Harvard Sussex Program draft treaty (*1*), which is designed to make an international crime out of involvement with chemical or biological weapons, thus outlawing them in a similar way to hijacking or torture. Another approach would be the biological research security system proposed by the University of Maryland's Center for International and Security Studies, a scheme for classifying levels of concern over experiments and providing international coordination of oversight for those deemed of extreme concern (*2*). These and similar initiatives offer hopeful alternatives to almost a decade of unilateral security solutions as exemplified in the building up of the U.S. biodefense research effort to its present colossal, and probably counterproductive, proportions.

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EDUCATION

The Nation's Report Card: A Vision of Large-Scale Science Assessment

The 2009 National Assessment of Educational Progress uses an expanded variety of tasks to probe student science achievement.

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Results from the 2009 National Assessment of Educational Progress (NAEP)—the "Nation's Report Card," a leading measure of U.S. student achievement in many subjects at grades 4, 8, and 12—will provide new insight into what students know and can do in science (*1*–*3*). In anticipation of the 2010 release of those science results, we highlight related resources (*1*, *4*, *5*), and how a new NAEP science framework attempts not only to reflect the last 20 years of science and science education but also to signal the way forward and push the boundaries of large-scale science assessment.

The previous science framework was developed in the early 1990s before publication of some prominent national efforts to improve science education (*6*, *7*). The 2009 framework (*8*), which may be used through 2021, not only reflects these standards but also takes into account standards in international science assessments (*9*, *10*). Major strengths of the 2009 NAEP, as well as some limitations, are summarized in the table on page 1638. (See table S1 for a summary of differences between the 2009 and 2005 frameworks.)

Science Content and Practices

In specifying what will be assessed, NAEP signals what educational outcomes are valued. Yet, like any large-scale assessment that requires standardization and limited student response time, NAEP cannot capture all important outcomes regarding depth of knowledge and aspects of inquiry.

To assess some core science concepts in depth, the framework organizes content into three areas: Physical Science, Life Science, and Earth and Space Sciences. But, what individual students know and can do—their cognition and understanding of content—cannot be measured directly; this must be inferred by interpreting observable behavior (*11*). Thus, good assessments hinge on sound cognitive models of how individuals learn and represent their knowledge. For example, compared with novices in a domain, experts have highly organized knowledge structures (*12*); knowledge is "constructed," not simply "poured" into one's head. Such research guides the design of the 2009 framework, working from a cognitive model of achievement to define in observable terms what students should be able to do with content.

To this end, the NAEP framework identifies four science practices (*5*). Identifying Science Principles and Using Science Principles, the first two, describe how students know science, for example, relating science concepts (e.g., temperature and state of matter) and predicting observations of phenomena (e.g., what happens to an object's speed as it rolls downhill). Third, Using Scientific Inquiry describes practices and understandings relating to the nature of science and how scientists work (e.g., conduct and critique scientific investigations and relate patterns in data to theoretical models). Fourth, Using Technological Design emphasizes how science knowledge and skills are used to solve design problems (e.g., how to minimize ecological effects of fertilizer runoff). By combining the four science practices with the three science content areas, developers pinpoint observable behaviors of interest, which guide development of appropriate assessment items.

New Types of Assessment Tasks

Traditionally, large-scale assessments have relied on conceptually disconnected multiple-choice and short-answer items, efficient for assessing recall of discrete facts, application of appropriate formulas, and critiquing written procedures. However, these are not ideal for assessing such practices as relating multiple concepts, explaining scientific phenomena, conducting a physical investigation, and manipulating variables in a dynamic simulation. To address this, the 2009 framework breaks new ground with item types (*5*, *13*).

Recommended for inclusion but never before used on NAEP science assessments, concept maps require students to draw and describe connections among science concepts (fig. S1). Students use labeled, directional arrows to link pairs of concepts (e.g., chloroplasts, green plants, and photosynthesis) and explain the relations among them (e.g., "requires" or "contains"). Moving beyond concepts in isolation, these valid, reliable instruments (*14*, *15*) allow students to represent the structure of their science knowledge.

An item cluster uses research on how students conceive phenomena [e.g., in force and motion (*16*, *17*)] by centering a set of related items on a scientific phenomenon and probing students' "mental models" about it (fig. S2). A single multiple-choice item (e.g., "What forces act on an object at rest?") can draw its incorrect options from alternative, inaccurate conceptions known to be held by students (e.g., "If an object is at rest, then no forces are acting on it.") (*18*). Analyses of responses across items in a cluster provide reliable, valid insights into how students make sense of scientific phenomena [e.g., (*19*)].

Predict-Observe-Explain items ask students to make predictions about a presented situation and, following an observation or summary of what actually happens, ask students to provide explanations (*20*). For example, students might be asked to predict whether a given object sinks or floats in water. Once they find out that the object sinks, they must explain why this occurred. This provides opportunities to reliably capture how students reason through and justify their predictions and explanations (*21*).

Used on past NAEP science assessments, hands-on performance tasks (HOTs) are reliable, valid (*22*, *23*) probes of knowledge and skills related to scientific inquiry. Presented with a challenge, students must find a scientifically justifiable solution by selecting from and manipulating physical materials provided by NAEP. To prevent them from being like recipes, tasks should be rooted in science principles and open-ended enough for students to determine their own investigative procedures (*24*). For example, students might use batteries, bulbs, and wires to develop procedures for identifying the contents of "mystery boxes" (fig. S3) (*25*).

In 2009, for the first time, NAEP used computers for assessment. Interactive computer tasks (ICTs) hold potential for trans-

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Strengths and Limitations of the 2009 NAEP Science Assessment

Strengths

- Resource for local, state, and international curriculum and assessment as it reflects national standards (*6*, *7*), research on how students learn, and broad-based input and expertise
- New types of assessment items improve probes of breadth and depth of science knowledge and practice
- Developed with sophisticated methodology that included internal and external reviews and pilot testing
- Monitors student achievement over time and at national, state, and selected urban district levels
- Allows comparisons across student subgroups (e.g., gender, race and/or ethnicity)
- Reports results as both average scaled scores and percentages of students attaining basic, proficient, and advanced achievement levels
- Public release of detailed reports, sample assessment items, student responses, scoring guides, student background variables, and other data and software tools for secondary analyses

Limitations

- Does not measure attitudes, beliefs, affect, or skills such as creativity, collaboration, and social responsibility
- Limited resources and time prevent measurement of all important outcomes, limiting the definition of scientific inquiry and technological design
- New types of assessment items require considerable time and costs for development, administration, scoring, and analysis
- Safety and practical concerns limit student access to certain physical materials and equipment during testing
- Does not monitor or report student achievement at individual student and school levels
- Does not report subscale scores on science practices or types of items
- Low stakes for students may reduce motivation and participation rates

forming testing but are the least psychometrically studied of the item types (*26*). The framework describes four categories of ICTs (*5*, *27*) (fig. S4). First, information search and analysis requires searching a database, selecting relevant information, and applying it to a problem (e.g., research the scientific tradeoffs of building a dam). Second, empirical investigations move HOTs to a computer platform, useful when investigations with real materials are not feasible (e.g., conduct experiments involving hazardous chemicals). Third, simulations allow students to reason with and manipulate models of scientific phenomena that may otherwise be inaccessible (e.g., erosion and molecular motion occur over difficult-to-observe time and spatial scales). Last, concept mapping on computers may alleviate logistical challenges associated with paper-and-pencil mapping tasks (*28*).

Interpretation, Implementation, Iteration

What NAEP can reveal about student achievement depends on how scores are constructed and reported. NAEP has typically reported subscale scores for content areas but not for practices (e.g., we can compare achievement across Physical and Life Sciences, but not across Identifying Science Principles and Using Technological Design) (*29*). Unless performance is adequately reported, valid interpretations of NAEP scores remain limited. The framework developers recommended reporting subscales for both content and practices, and releasing examples of new item types (*30*, *31*).

The results of the 2009 NAEP are not yet publicly available, so we must trust that the assessment stays true to the framework outlined here. But it is no simple task for this vision to be faithfully interpreted and conveyed through a complex implementation process. The National Assessment Governing Board, the National Center for Education Statistics, and their contractors have developed new items, administered the assessment, scored student responses, and are now finishing analyses and preparing reports. Evaluations of the framework and assessment will occur as interested researchers analyze NAEP data (*32*).

As NAEP builds capacity in innovative assessment tasks, we expect it to evolve with future iterations. It is up to the public and all those who have a stake in science education to consider not only the NAEP results but also the quality of the assessment itself, to press for assessment that is ever truer to the breadth and depth of what it means to achieve in science.

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1. NAEP, http://nces.ed.gov/nationsreportcard/.
2. Over its 40-year history, NAEP has tracked students' science achievement roughly every four years (*3*). NAEP frameworks are generally used for three or four assessment cycles.
3. Different purposes of assessment include diagnosis, evaluation, program improvement, accountability, and monitoring. As large-scale snapshots of achievement, NAEP and international assessments, such as (*9*) and (*10*), fall primarily into the category of monitoring tools. This contrasts, e.g., with state-level science assessments in the United States, which typically measure achievement of individual students and schools for accountability purposes.
4. National Assessment Governing Board (NAGB), www.nagb.org/.
5. NAGB, *Science Framework for the 2009 National Assessment of Educational Progress* (U.S. Government Printing Office, Washington, DC, 2008); http://nagb.org/publications/frameworks/science-09.pdf.
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8. To develop the 2009 NAEP Science Framework, an independent, bipartisan board (*4*) appointed by the Secretary of Education convened scientists, educators, education researchers, assessment experts, government officials, industry representatives, and members of the general public (*5*, *30*); all authors were actively involved in these efforts.
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27. Neither ICTs nor HOTs are administered to the entire student sample in recognition of the additional time required to administer, score, and analyze these more complex tasks.
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31. HOTs and ICTs will be excluded from scaled scores for technical and practical reasons, though a special report is expected to provide extra information. Personal communication with S. Loomis, Assistant Director for Psychometrics at NAGB; www.nagb.org/who-we-are/staff.htm.
32. There likely will be discussion about the quality of the assessment, although this may be difficult to judge, because most test items are kept secure from the public to allow repeat use in the next round of testing.
33. The views expressed in this article are those of the authors and do not necessarily represent the views of the organizations or agencies that provided support for the framework development project.

Supporting Online Material

www.sciencemag.org/cgi/content/full/326/5960/1637/DC1

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EVOLUTION

Sexual Selection and Darwin's Mystery of Mysteries

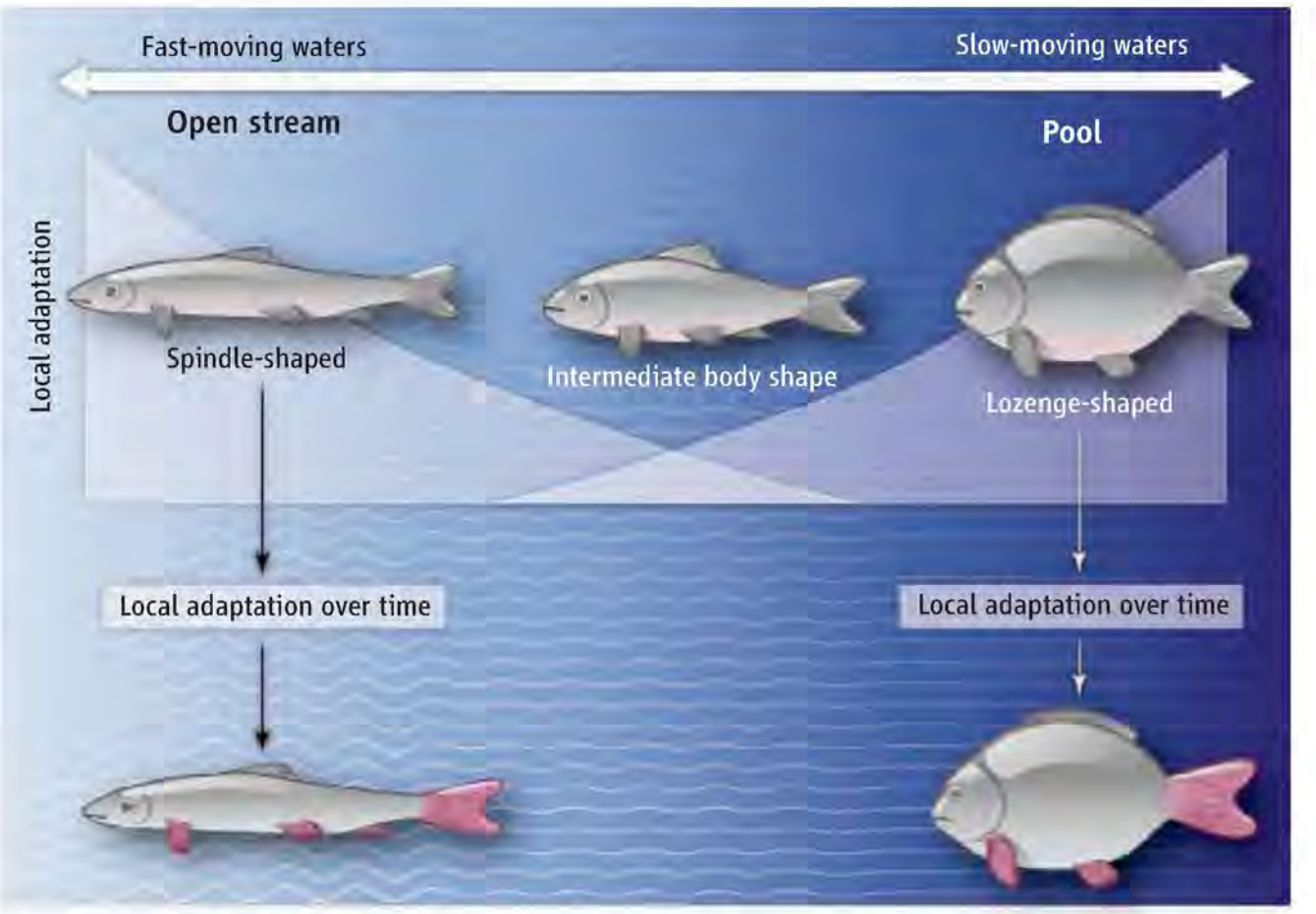
Natural selection and mating preference for traits that signal adaptation to the local environment work together in a model of speciation.

Judith E. Mank

Darwin referred to the origin of species as "that mystery of mysteries" (*1*), and despite decades of study, evolutionary biologists still cannot agree on the underlying processes that have produced the great diversity of life around us. Most contentious of all has been the question of whether speciation can occur within a population (sympatrically). On page 1704 of this issue, van Doorn *et al.* (*2*) suggest that mating preferences can halt the movement of genes within a population. Their work gives credibility to the concept of sympatric speciation, which has long been the ugly duckling of evolutionary biology, and suggests that both local adaptation and sexual selection may play a far more important role in speciation than previously thought.

The traditional model of speciation is based on geographic isolation, in which a single population is divided by some geographic barrier, halting gene flow. Each group gradually changes over time, resulting in two separate and genetically distinct populations. This buildup of genetic incompatibilities will act as a barrier to the production of hybrid offspring, resulting in separate species (*3*). There is very little debate about whether speciation occurs by this allopatric model, as biogeography offers many striking examples. Island endemic species, such as Darwin's finches, diverged from mainland ancestral species after long periods of isolation (*4*). Pairs of morphologically similar species (geminate species) found in the Caribbean and Pacific oceans resulted after the Isthmus of Panama cut off gene flow in marine animals (*5*). What has remained unclear is whether this biogeographic model of speciation is the only, or even the dominant, mechanism by which new species originate.

Sympatric speciation is theorized to occur when selection pressures favor the extreme phenotypes at the expense of the intermediate ones (*6*), presumably due to local ecological variation. Without some mechanism to prevent mating between different phenotypes, individuals with the intermediate, unfavorable, traits will be created in every generation, and the subpopulations will be unable to diverge and adapt to their local ecologies. Because it has been difficult to build viable population genetic models of how gene flow might be curtailed in the absence of a geographic barrier, sympatric speciation has been regarded with a great deal of doubt by most evolutionary biologists ever since it was dismissed by Ernst Mayr (*7*) and Theodosius Dobzhansky (*8*).



Sexual selection and local adaptation. In this example, fast-moving currents in open streams select for a fusiform-shaped body, whereas deeper shapes are advantageous in pools with slow currents. Intermediate shapes are poorly adapted to both environments. Locally adapted males are in good condition, and therefore exhibit long, bright fins that are the basis of female mating preferences. Over time, female preference for the condition-dependent sexually selected trait is strengthened; therefore, fewer individuals of intermediate body shape are generated. Eventually, genetic incompatibilities accrue and prevent the formation of fertile hybrids despite continuous and uninterrupted sympatry.

Speciation has been shown to occur in areas that are too small to contain real barriers to gene flow (*9*), giving credence to the possibility of sympatric speciation. However, because the allopatric model is assumed to be true, demonstrating sympatric speciation requires irrefutable proof that daughter species were never geographically isolated—a burden of evidence that is seldom met. However, this does not mean that sympatric speciation is truly rare; rather, it is rarely proved beyond a doubt.

Van Doorn *et al.* provide a way forward by building on the observation that mating preferences can accelerate rates of speciation (*10*, *11*) and maintain local adaptations in the face of potential gene flow (*12*). The key to their advance is the incorporation of condition-dependent mate choice. Past attempts to model sexual selection and sympatric speciation were based on the idea that female mating preferences were heritable but arbitrary. In their treatment, the authors assume that male traits preferred by females are a product of local adaptation (*13*).

A male in good condition is well adapted to his local environment, and he demonstrates this with a condition-dependent male "ornament," such as bright fins in fish (see the figure). A female that prefers males with this ornament has a mechanism to identify and select locally adapted mates, increasing the probability that her offspring will also be well suited to the local ecology. Nat-

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ural selection and sexual selection act as a positive-feedback loop, strengthening both local adaptation and female preference for the sexually selected trait. This allows specialization even when the organisms overlap within a contiguous range. Over time, the populations diverge and ultimately form separate species.

Van Doorn *et al.* thus overcome a major stumbling block by providing a viable model of sympatric speciation. Species originating under this model may bear a certain signature that can be used to determine the prevalence of sympatric speciation via condition-dependent sexual selection. These sister species will specialize on distinct ecologies that overlap geographically. Further, males in all specialized daughter species will exhibit similar types of condition-dependent sexual ornaments. In early stages of speciation, mating preferences will be the primary barrier to gene flow, and the removal of this will result in the loss of local adaptation as the daughter populations interbreed and revert to the overall population mean. Finally, because condition-dependent sexually selected traits are a driver of speciation, clades with these ornaments will be more species-rich than clades with sexually selected traits that are condition-independent, or clades that lack male ornaments entirely.

This model may be used to test the prevalence of local adaptation and condition-dependent sexual selection in generating diversity, and provides a means to bring sympatric speciation in from the cold.

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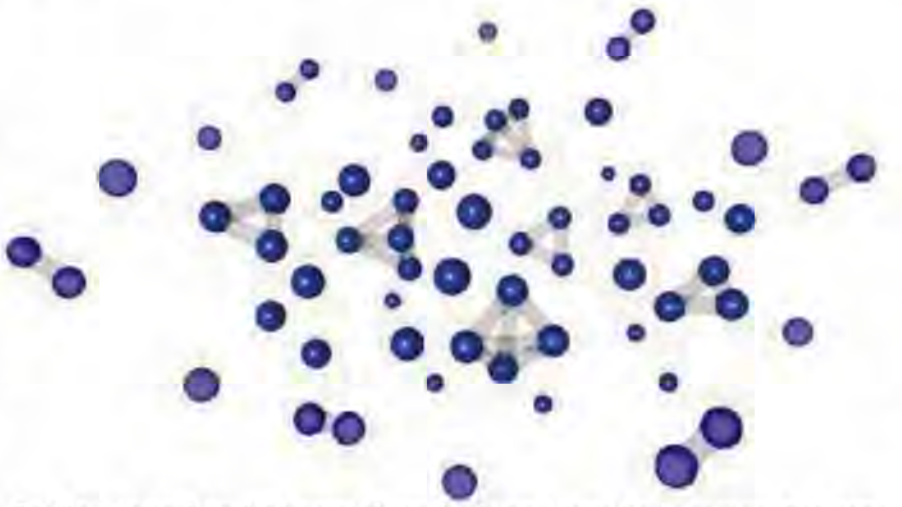
10.1126/science.1184680

PHYSICS

Universal Few-Body Binding

Cold atoms are providing insights into binding processes within systems of a small number of interacting particles.

Giovanni Modugno



Getting together. Universal three-body and four-body composites naturally form in an ultracold gas of lithium atoms with resonant interaction. They are detected as they decay into hot atoms and dimers (light blue), which rapidly leave the ultracold sample.

Predicting the binding rules of quantum particles is a formidable task. Even for as few as three particles, one would need to know precisely all the details of the mutual interactions among them. Notable exceptions have been predicted to arise if the interaction between the particles is very large, a condition where universal binding laws are expected to appear (*1*, *2*). Because no available physical system composed of atoms, nuclei, or even elementary particles was suitable to observe the phenomenon, these ideas have been mainly confined to theory. On page 1683 of this issue, Pollack *et al.* (*3*) present evidence for the presence of universal scaling laws simultaneously occurring for three- and four-body bound states in an ultracold atomic system. The observation confirms both old and new theoretical predictions, thus providing a fuller understanding of universal binding.

Since the early days of quantum mechanics, there has been great interest in deriving from first principles how particles bind together, particularly in the context of nuclear physics. A special solution to this problem was proposed for the case of three particles by Vitaly Efimov in 1970 (*1*). It was shown that if the interaction length between pairs of particles (the so-called scattering length) is much longer than any other length scale in the system, then the binding is universal—that is, it depends only on that length. In this regime, the three-body problem admits a whole series of states whose basic properties, such as the energy, follow geometrical scaling laws with a single scaling factor that can be derived analytically from the theory (*4*).

Early work on ultracold atomic systems has shown that a window to observe such binding behavior might exist (*5*), thanks to the possibility of engineering resonantly large scattering lengths between the atoms (*6*). This is achieved via the Feshbach resonances, whereby a magnetic field is applied to the sample to change its interaction properties. By means of such a technique, a universal bound state of three identical bosonic particles (an Efimov trimer) was observed in a sample of ultracold cesium atoms (*7*). There has since been a tremendous acceleration of the field, with major results in both experiment and theory. Notable examples are the observation in potassium atoms of two consecutive trimer states featuring a scaling very close to the one originally predicted by Efimov (*8*), and the prediction and experimental verification of universal scaling laws for four-body states (*2*, *9*).

In the ultracold lithium atom system studied by Pollack *et al.*, the scattering length can be resonantly changed over a large range of values. By studying the rate at which the atoms are lost, two Efimov trimer states, each of them with two four-body states attached, that follow quite closely the universal scaling laws have been identified. The measurements are very precise, allowing the universal scaling factors to be nailed down. In addition, there are unexpected details in the observations that might provide new clues to verify the peculiar properties predicted by theory.

This is not the end of the quest for universal binding laws, however. The very precise work by Pollack *et al.*, together with other recent measurements including those performed on a different internal state of the same lithium atoms (*10*), show that not everything fits the

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universal scaling theories. Thus, the theory needs to be further developed—for example, to consider not only interactions between pairs of particles, but also the simultaneous interaction of the three of them. There is also the need for new and better experiments that can probe more properties of these systems.

Even after a century of research, there remains excitement in understanding the few-body binding laws. Besides the interest in identifying simple universal relations, there is another important motivation for those working with ultracold atomic gases: One goal is to be able to engineer the interaction between atoms to achieve a quantum system in which multiple-body interactions dominate the physical behavior (*11*). Because the dominant contribution has so far come from two-body interactions, this would lead to a revolution possibly opening new avenues for fundamental research—for example, in the study of exotic quantum phases (*12*).

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PSYCHOLOGY

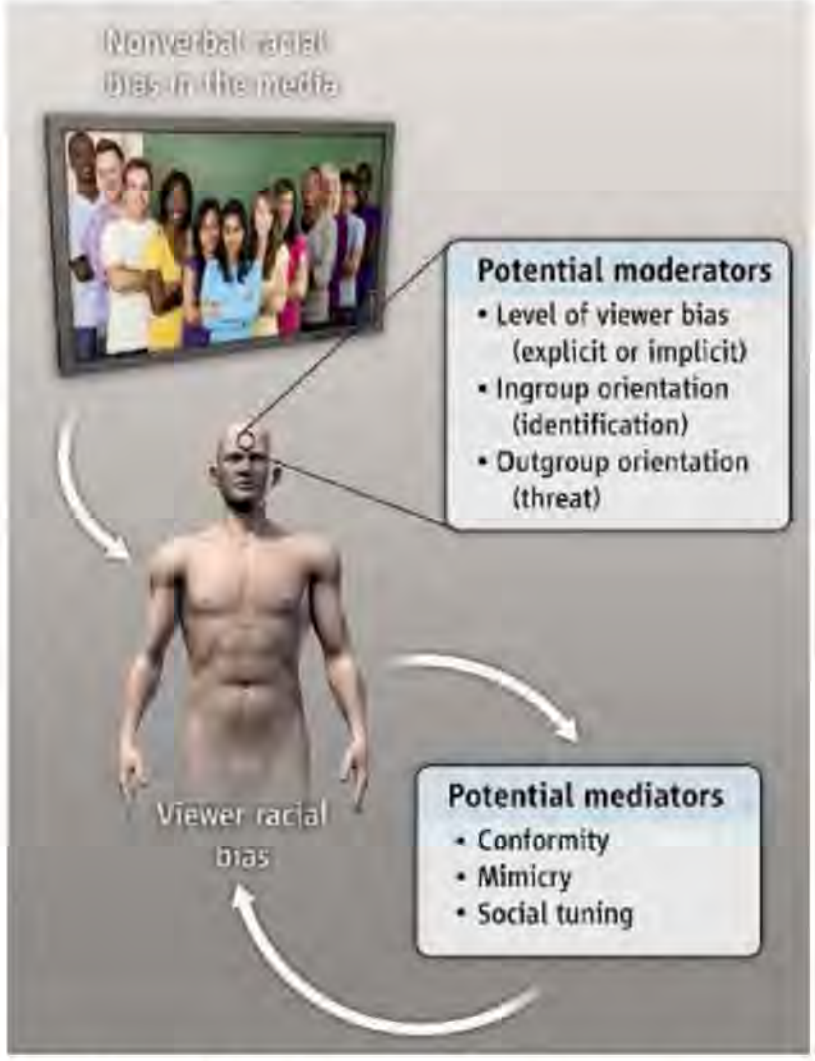
Racial Bias, Unspoken But Heard

Exposure to nonverbal behaviors can transmit race bias to observers.

John F. Dovidio

Nonverbal behavior is a powerful form of social influence. People can abstract accurate meaning from even very brief exposures to nonverbal behavior—a facial expression or subtle body language, for example (*1*). Across cultures, the ability to understand nonverbal messages occurs quickly; even infants and toddlers demonstrate this capacity. Moreover, nonverbal signals can be especially effective in transmitting social attitudes because they can be spontaneously understood with minimal effort and are perceived as a source of valid information. On page 1711 of this issue, Weisbuch *et al.* (*2*) examine how racial prejudice can be covertly spread and reinforced, and propose that in American society, negative nonverbal behavior modeled by white individuals in popular media critically shapes white viewers' orientations toward black individuals [see (*3*) for how race was determined in the study].

Norms of egalitarianism in the United States have grown steadily stronger, while expressed racial prejudice among white Americans has declined dramatically (*4*). Yet, there is ample evidence that whites continue to exhibit bias against blacks (as well as toward other traditionally disadvantaged groups), not only with respect to the extremist behaviors of an unrepresentative few but also in terms of subtle discrimination by a substantial portion of mainstream white American society (*5*). The dynamics of subtle bias have received substantial empirical attention and are generally well understood. For example, whites who appear nonprejudiced on self-report measures tend to display negative nonverbal behaviors as a function of unconscious, automatically activated racial bias (*6*). Less clear, however, is how this prejudice, which is largely unspoken, can be transmitted culturally. The findings of Weisbuch *et al.* are particularly provocative because they uncover racial bias in actors' nonverbal displays despite the highly scripted nature of prime-time television shows, which generally minimizes expressions of racial bias (*7*). In addition, they obtain their findings with samples of white college undergraduates, who are more favorable toward outgroups (individuals whom the white students consider outside their group) and more inclined to conceal negative responses toward outgroups than the "average" white American (*8*). Thus, nonverbal messages influence relatively sophisticated participants who are especially motivated to appear unbiased.



Covert transmission. An individual's implicit prejudice, ingroup racial identity, and current state of intergroup relations can increase his/her sensitivity to nonverbal cues of bias, such as those displayed on television. These cues, in turn can shape viewers' perceptions of social norms or induce mimicry or social tuning to elicit personal racial bias.

Although Weisbuch *et al.* demonstrate the potent impact of viewing nonverbal expressions of racial bias in the media, they do not directly illuminate the processes that account for this influence. It is possible, for example, that despite their conscious motivation to appear unbiased, participants actually harbored prejudice toward blacks. Thus, they may be particularly attuned to nonverbal expressions of racial bias, which could disinhibit their latent (implicit) prejudice. Indeed, participants in the Weisbuch *et al.* studies showed an overall prowhite bias on an implicit association test, which is hypothesized to measure the strength of automatic mental associations between objects and/or concepts. In addition, exposure to the racially biased nonverbal behavior on television influenced

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their spontaneous emotional responses to blacks but not to Asians. This explanation suggests that the impact of viewing nonverbal bias against blacks on television would be more pronounced among whites who have stronger implicit antiblack dispositions.

The findings of Weisbuch *et al.* also implicate the more general process of social tuning (*9*). As social animals, humans strive to establish a sense of shared reality with others; consensual understanding has the psychological benefit of reducing uncertainty and social anxiety, as well as the practical consequence of enhancing coordination. Because of the primacy, efficiency, and immediacy of nonverbal communication, nonverbal signals can elicit similar responses. People spontaneously mimic the nonverbal behaviors of others (*10*). From the social tuning perspective, the impact is deeper than behavioral mirroring: People also adopt the views that the other person is perceived to hold, particularly when there is an affiliative bond with the other person.

Group identities can also influence the ways people attend and respond to nonverbal expressions of others in systematic ways. People automatically evaluate other members of their group (ingroup members) more positively, are more trusting of them, and process information about them in a deeper and more detailed way. Members of other groups are viewed with suspicion and competitively (*11*). As a consequence, people may be especially sensitive to nonverbal cues from a member of their own racial group, particularly when it signals something negative about a member of another group. Shared group membership further provides the affiliative connection that motivates social tuning, which occurs without full awareness or control. In the United States, people automatically activate mental representations of racial group memberships when they see a person of another race. They become spontaneously aware of the person's racial group membership, which makes them also think more about their own group membership. However, because Weisbuch *et al.* used only white participants, it is unclear whether their participants' behaviors are rooted specifically in whites' prejudice toward blacks or represent a more general intergroup phenomenon. In the latter case, the effects of witnessing an ingroup member display negative nonverbal bias would occur both for blacks and whites and be stronger when participants have stronger group identities or feel more threatened by the outgroup.

Thus, the nonverbal displays of white characters toward blacks on television have deep influence on the whites' attitudes toward, and associations with, blacks. Beyond its practical implications, including illuminating how unspoken racial bias can be transmitted to millions of white Americans, the research of Weisbuch *et al.* suggests that nonverbal signals of ingroup members toward outgroup members can have a profound impact on white Americans' biased behavior—one that occurs largely without awareness. The influence of nonverbal racial bias on television evades the normal strategies for inhibiting overt manifestations of bias and can be communicated widely in unspoken ways to have broad impact on intergroup relations.

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ENGINEERING

Enabling New Missions for Robotic Aircraft

Improved sensing and planning for enhanced flight duration allow unpiloted small aircraft to fly autonomously in cluttered environments over long distances.

Jack W. Langelaan[1] and Nicholas Roy[2]

Can we engineer an artificial "homing pigeon"—that is, create a small aircraft that can perform a task for us, pilot itself, and travel for a long time over great distances? Uninhabited aerial vehicles (UAVs), which have been developed mainly for military applications, are still remotely controlled, and some tasks, such as flying in crowded environments, are too difficult, dangerous, or expensive to be performed by even the smallest of these aircraft (*1*). These problems have spurred the development of smaller robotic air vehicles. Specifically, micro air vehicles (MAVs) are inexpensive, fly autonomously, and are small and lightweight (with wingspans of 15 cm or total mass of 0.5 kg) (*2*). We focus on the two technical challenges that must be met by MAVs if they are to fly as well as birds, namely perception—sensing and responding to their environment—and persistence—staying airborne.

MAVs possess special features that allow them to perform missions that cannot be completed by larger aircraft. For example, MAVs can fly in close proximity (0 to 50 m) to terrain where collision risks are high, and can collect data in urban or dense forest environments. For atmospheric studies, conventional aircraft create more disturbances on airflow and need long sensor booms or towed arrays. An MAV has little effect on airflows, and sensors can reside on the aircraft. Additionally, MAVs can operate stealthily, allowing both covert military surveillance missions and surveillance of natural animal behavior in places where larger UAVs cannot operate.

Perception is essential for MAVs operating in new flight domains, not only to execute their mission but also for basic guidance and control. The main issue is that capabilities are dictated by the payload capacity of the craft, and the ability to lift payload is limited by small wings. The navigation systems for larger UAVs are designed under the assumption that position and velocity are known at all times. They rely on both a global posi-

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tioning system (GPS) and highly accurate but heavy inertial measurement units (IMUs). The latter provide the necessary position and velocity estimates and are in effect an electronic version of a sailor's "dead reckoning."

A different approach must be taken with MAVs, which cannot carry highly accurate inertial sensors and would operate indoors or between buildings ("urban canyons") where GPS signals can be degraded or lost. An MAV must estimate its position and velocity with respect to the local environment using sensors such as range finders or cameras. It also must track its position against an onboard map of the terrain, or build one as it moves.

Flying in tight quarters. A video shows the flight of a rotary wing MAV that carries an inertial measurement unit, a compass, a GPS receiver, a laser range finder, and multiple cameras. When GPS is unavailable, the MAV can use the onboard sensors to both map the environment and estimate its position.

Until recently, MAV perception has been limited to environments with accurate GPS and a few simple obstacles (*3*). However, smaller hardware should enable the use of methods developed for ground-based robots for simultaneously estimating vehicle position and creating an environmental map (*4*, *5*). Such methods were developed 10 to 15 years ago, but only recently have some of the sensors used, such as laser range finders, been miniaturized so that they can be carried on an MAV. The range and field of view of these sensors make any single estimate of the world geometry incomplete, but statistical inference techniques that aggregate the data over time can overcome these limitations (*6*) (see the first figure). All of the mapping, position estimation, guidance, and control processes that generated this map were performed onboard the MAV. In a first-response scenario, an MAV would enter and explore a building, and relay images of the building interior to people stationed outside.

Ongoing research in ground robotics is leading to autonomous vehicles that can learn world models that have embedded semantics (*7*, *8*). They not only map free space and obstacles, but also can segment the world into objects or regions, and label them in the same way that people do. An MAV with similar capabilities could recognize and use an open window to enter a building, identify and locate objects or areas within it, and accept natural-language instructions from human operators (*9*). However, the statistical inference required to learn and use these models is not feasible on the current computational platforms that can be carried by MAVs for reasons of weight and power. As central processing units continue to become smaller, lighter, and more power-efficient, the perceptual capabilities and mission capabilities of MAVs will continue to grow.

Like small ground-based robots, MAVs suffer from limited capacity for onboard energy storage. There is often an explicit trade-off between fuel (for increased mission duration) and sensing payload (for increased data collection). Smaller sizes also lead to aerodynamic penalties, because viscous drag forces, such as skin friction, are relatively more important. Together, these two factors greatly reduce the mission capabilities (and hence utility) of small robotic aircraft.

One way to extend operational lifetime is to fly more like a large bird or a glider. Soaring flight enables a bird or aircraft to harvest energy (in the form of increased altitude or speed) from the atmosphere and greatly extend flight duration and distance. Research on this topic dates to studies by Lord Rayleigh (*10*). Three conditions allow for energy harvesting—vertical air motion, spatial gradients in the wind field, and temporal gradients (wind gusts). These phenomena occur at different time scales and require different degrees of control in order to be exploited.

Vertical air motion is exploited by hawks, vultures, and eagles (as well as human sailplane pilots). Flight times can extend to hours, and distance to hundreds of kilometers, without flapping wings (or using engines). There are three main sources of this air-mass movement. Uneven heating of the ground produces buoyant instabilities called thermals. Long-period oscillations of the atmosphere cause a vertical motion, or "wave." Finally, wind is deflected by the slopes of hills and mountains to create orographic lift.

Compared with the speed of aircraft dynamics, vertical air motion is a quasi-static phenomenon, and flight that exploits vertical air motion is known as static soaring. Autonomous thermal soaring of a 4.3-m wingspan UAV was demonstrated by Allen and Lin (*11*) at Edwards Dry Lake Bed in the Mohave Desert of southern California. In contrast with thermals, which are not predictable with current meteorological models, vertical air motion caused by orographic lift (also known as ridge lift) or wave is predictable. Advanced trajectory planning techniques are being developed to use this a priori knowledge of the wind field to enable extremely long duration and distance flights (*12*). A prediction of regions where an MAV could gain energy while flying as an unpowered glider is shown in the second figure.

Exploiting spatial gradients in the wind field (a flight mode known as dynamic soaring) requires more aggressive flight, often in close proximity to terrain. Seabirds such as albatrosses exploit the spatial gradient in the wind field that exists near the ocean surface (*13*). Deittert *et al.* (*14*) discuss both optimal trajectories and the likelihood of finding favorable wind conditions for dynamic soaring by MAVs.

The third means of extracting energy from the air exploits gusts. Anecdotal evidence indicates that the flight performance of large birds is improved by gusts, but is typically reduced on human-piloted radio-controlled aircraft. Extracting energy from gusts is complicated by their typically short duration, so this difference in performance likely reflects the better sensory input and faster reaction times of the birds. Gust energy harvesting has

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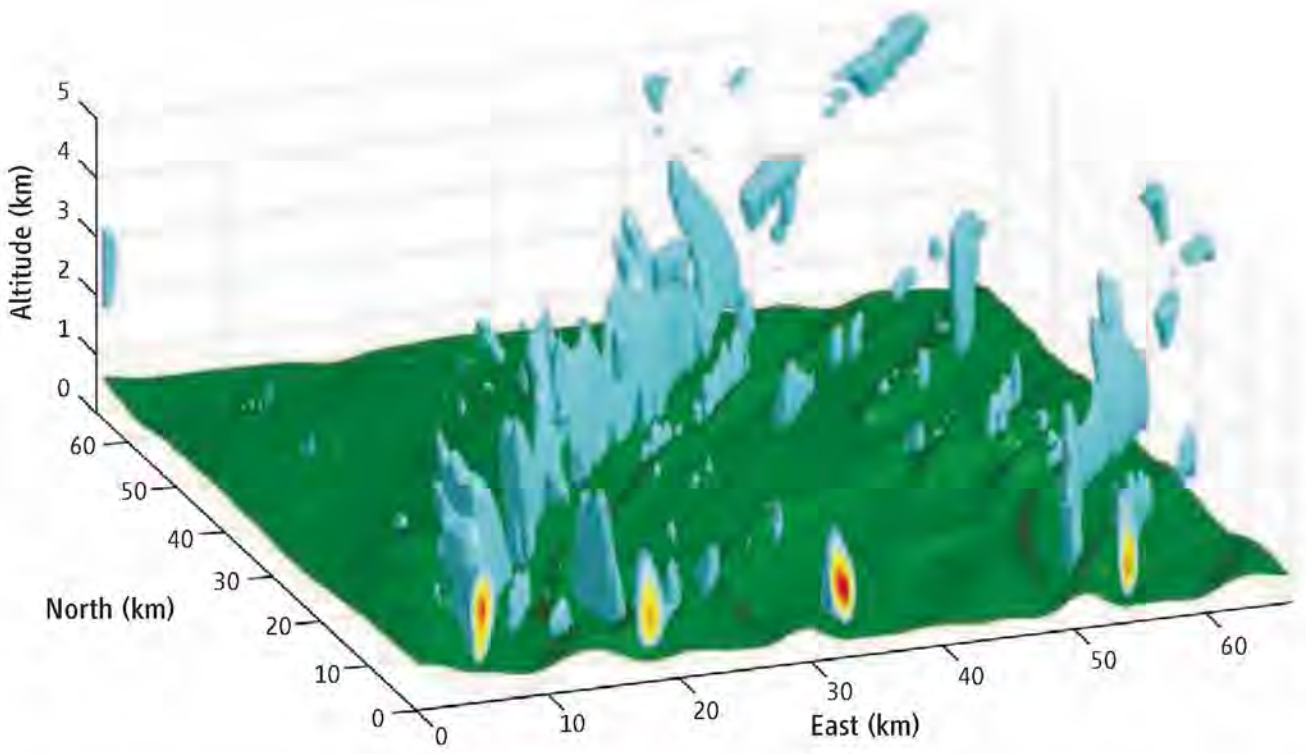
been demonstrated on a small UAV (*15*), and there is ongoing research in control strategies to improve cruise performance of small and mini-UAVs by gust energy harvesting.

The improved perception provided by the sensing and processing systems, coupled with the improved persistence provided by atmospheric energy harvesting, should enable long-endurance missions that are far beyond the capabilities of current robotic aircraft. Eventually a soaring-capable, autonomous, mini-UAV that is equipped with a sophisticated sensing system will be able to follow a migrating bird and provide close-up in-flight video, as well as in situ atmospheric measurements. Successful completion of such a challenging mission would demonstrate that flight by human-built robotic aircraft could rival that of birds.



Wind-assisted outdoor flight. The potential for extracting energy for flight from natural winds created by mountain "wave"—long-period oscillations of the atmosphere—over central Pennsylvania (Allegheny Plateau, Bald Eagle Ridge, and Tussey Ridge). The cyan isosurfaces bound the regions where soaring can occur—vertical wind velocity exceeds the sink rate of the vehicle. Nighttime wind-field changes are shown in video S2.

CREDIT: (PLOT) A. CHAKRABARTY/DEPARTMENT OF AEROSPACE ENGINEERING, PENN STATE UNIVERSITY. (DATA) G. S. YOUNG, B. J. GAUDET, N. L. SEAMAN, D. R. STAUFFER/DEPARTMENT OF METEOROLOGY/PENN STATE UNIVERSITY

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Supporting Online Material

www.sciencemag.org/cgi/content/full/326/5960/1642/DC1
Videos: S1 and S2

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COMPUTER SCIENCE

Mining Our Reality

Tom M. Mitchell

Real-time data on the whereabouts and behaviors of much of humanity advance behavioral science and offer practical benefits, but also raise privacy concerns.

Something important is changing in how we as a society use computers to mine data. In the past decade, machine-learning algorithms have helped to analyze historical data, often revealing trends and patterns too subtle for humans to detect. Examples include mining credit card data to discover activity patterns that suggest fraud, and mining scientific data to discover new empirical laws (*1*, *2*). Researchers are beginning to apply these algorithms to real-time data that record personal activities, conversations, and movements (*3*–*8*) in an attempt to improve human health, guide traffic, and advance the scientific understanding of human behavior. Meanwhile, new algorithms aim to address privacy concerns arising from data sharing and aggregation (*9*, *10*).

To appreciate both the power and the privacy implications of real-time data mining, consider the data available just to your phone company, based on your phone records and those of millions of other individuals who are going about their daily lives carrying a smart phone—a device that contains a Global Positioning System (GPS) sensor locating you to within a few meters, an accelerometer that detects when you are walking versus stationary, a microphone that detects both conversations and background noises, a camera that records where each picture was taken, and an interface that observes every incoming and outgoing e-mail and text message. The potential benefits of mining such data are various; examples include reducing traffic congestion and pollution, limiting the spread of disease, and better using public resources such as parks, buses, and ambulance services. But risks to privacy from aggregating these data are on a scale that humans have never before faced.

One line of research is based on watching where people are, where they are heading, and when. Anonymous real-time location data from smart phones are already being used to provide up-to-the-minute reports of traffic congestion in many urban regions through services such as Google Maps (*11*).

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This information could be used to relieve congestion by controlling traffic lights in real time, and to optimize public transport schedules. Pedestrian traffic can also be monitored through GPS smart phones, for example, providing data on which parks are most frequently used and for how long. Even census data might be continuously updated by observing where your smart phone spends most nights.

Aggregating such GPS geolocation data with other sources opens up a vast range of new possibilities, as well as new privacy issues. For example, if your phone company and local medical center integrated GPS phone data with up-to-the-minute medical records, they could provide a new kind of medical service: If phone GPS data indicate that you have recently been near a person now diagnosed with a contagious disease, they could automatically phone to warn you.

A second line of research uses real-time sensing of routine behavior to study interpersonal interactions. For example, Pentland (*3*) has used specially designed work badges—"sociometers"—to study productivity and creativity in the workplace. The sociometers contain infrared sensors, microphones, accelerometers, and location sensors to record the location and duration of conversations between workers, their physical distance apart, who speaks when, speaker intonation, gestures, and upper body motion. Analyzing these data allows Pentland to track various informal and sometimes subconscious cues in conversations, such as the subconscious mimicry by one person of the head nods, gestures, and vocal intonations of the other.

In one study of salary negotiations between individuals monitored by sociometers, this subconscious mimicry was found to be a key indicator of successful negotiations, and was strongly correlated with the feelings both parties reported about their negotiation. Pentland calls such subconscious cues "honest signals" that can indicate how the conversation will turn out—even better than the actual words exchanged. This research, together with the growing collection of individual data on a vast scale, suggests an important new opportunity for behavioral psychology and social science (*4*): research based on large-scale field data collected as people go about their daily lives, in contrast to laboratory experiments that produce more controlled and more limited data.

A third line of research involves monitoring real-time cyber data to track the ebb and flow of interests and ideas of millions of individuals. For example, the Google Trends Web site (*12*) can be used to plot how many people queried Google for a given topic, broken down by year and date, and by country and city of origin. Ginsberg *et al*. have shown (*5*, *6*) that by mining millions of geographically localized health-related search queries, one can estimate the level of influenza-like illnesses in regions of the United States with a reporting lag of just 1 day—faster than the estimates provided by government agencies such as the U.S. Centers for Disease Control and Prevention (CDC).

Analysis of such cyber data allows new types of questions to be asked and answered. For example, Leskovec *et al*. (*7*) analyzed 10 million postings to 45,000 different blogs over a 1-year period to study the cascading spread of ideas in the blogosphere. The authors developed a computer algorithm to identify the blog routes through which new ideas most often spread, and calculate which handful of blogs out of these 45,000 one should read to maximize the probability of spotting relevant new topics quickly.

As more diverse sensors become pervasive, wireless networking becomes more widespread, and new algorithms are developed, a global sensor network monitoring much of humanity might emerge. The development and use of privacy-preserving data mining algorithms (*9*) will thus be very important. One promising approach based on secure multiparty computation (*10*) allows mining data from many different organizations without ever aggregating these data into a central data repository. Each organization performs part of the computation based on its privately held data, and uses cryptography to encode intermediate results that must be communicated to other organizations performing other parts of the computation. Such methods could, for example, be used to mine private medical records held at thousands of individual hospitals to determine which treatments work best for a new flu strain while retaining complete privacy of patient records within each hospital. Other privacy-preserving methods are also being explored, ranging from sharing only statistical summaries of the individual data sets, to inserting random perturbations into individual data records before sharing them.

Perhaps even more important than technical approaches will be a public discussion about how to rewrite the rules of data collection, ownership, and privacy to deal with this sea change in how much of our lives can be observed, and by whom. Until these issues are resolved, they are likely to be the limiting factor in realizing the potential of these new data to advance our scientific understanding of society and human behavior, and to improve our daily lives.

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PRESIDENTIAL ADDRESS

Reflections On: Our Planet and Its Life, Origins, and Futures

James J. McCarthy

THE THEME OF THE 175TH ANNUAL MEETING of the American Association for the Advancement of Science (AAAS), "Our Planet and Its Life, Origins, and Futures," celebrated an enormous breadth of scientific accomplishments that transcends many subdisciplines of the natural and social sciences. It was intended to be both a reflection on what has been learned and a look forward to what must yet be better known if we are to make wise choices as stewards of our planet. The program committee saw this as an opportunity to examine how we have come to know and understand the coevolution of life with its interacting biological, biogeochemical, and physical environments. Further advances in this area are essential to develop scenarios that can be useful in guiding decisions to address some of society's most pressing problems. We must work toward a future that embraces the wise application of science to improve human health and well-being and to sustain the great diversity of life on our planet.

The occasion of this annual meeting, which opened on the very day of the 200th anniversary of the birth of both Charles Darwin and President Abraham Lincoln, prompted special reflection on the significance of Darwin's contributions to our knowledge of the coevolution of organisms and their environment and the role that President Lincoln played in the advancement of science and, in particular, its application for the benefit of societal well-being. The meeting program was rich with papers and symposia that celebrated the 150th anniversary of Darwin's publication *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. Darwin's thesis was the product of decades of careful observations of the natural world, which he argued could be explained by natural selection. This year he is being properly heralded for his unequaled influence on our understanding of how life on Earth is sustained and how it changes to accommodate differing conditions over time. Today, even with our far more sophisticated understanding of the processes by which evolution occurs, Darwin's thesis remains robust. We now also know much more about how physical and chemical aspects of the environment for life have changed, and how inextricably life and its environment continue to coevolve. Regulatory aspects of feedbacks in the collective Earth system, between life and the physics and chemistry of the atmosphere, soils, and oceans, have provided a persistent habitable condition for a vast diversity of life over the past three billion-plus years.

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A profound lesson from the past few decades of scientific discovery across the Earth and life sciences is that the weight of the human footprint on essential life-supporting services of the Earth system has grown dramatically since the time of Darwin. Over the past 150 years, our population has grown fivefold. Our consumption of resources has grown even more. Some of this consumption has resulted in degraded conditions in terrestrial and coastal marine ecosystems that will, under the best of circumstances, persist for generations to come. Greenhouse gases released today by anthropogenic activities will affect the heat budget of Earth's atmosphere for tens of human generations. Some depleted aquifers will take even longer to recharge. For all intents and purposes, resources such as fossil oil have no prospect for regeneration on meaningful societal time scales. Species extinctions are irreversible.

Could Darwin have imagined that so soon in Earth history a single species would be altering the prospects for the survival of other species across all continents and to the greatest depths of the sea? Crutzen and colleagues suggest that this effect is sufficiently profound to declare that we have transitioned from the Holocene era of Earth history to the Anthropocene. Human population increased only 40% during Darwin's 73 years of life (from 1.0 billion to 1.4 billion). Someone today in her 73rd year would have witnessed a 300% increase in population over her lifetime. Demographic studies suggest that because of declining birth-rates across much of the developing world, a future doubling of today's population of 6.8 billion is unlikely. Most projections point to a leveling off of human population at 9 to 11 billion within the next two to three generations. The aggregate impact of our species on all others and on the systems that support us all in the future will, of course, depend not only on our population size but also on how we use Earth's resources.

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A 19th-Century Foundation for Climate Science

By remarkable coincidence, there were other notable findings and developments in 1859 that contribute to our knowledge of the Earth system and our capacity to alter it. In that year, the Irish chemist Sir John Tyndall discovered that CO_2 absorbs infrared energy as a radiatively active constituent in Earth's atmosphere. The quantitative relationship between CO_2 concentration and infrared absorption is very well established. In fact, a common way to measure the carbon content of plant and animal material is to combust a sample at high temperature. That process converts the carbon to CO_2, which is then quantified by its attenuation of an infrared beam passing through the chamber. Tyndall's work built on that of Joseph Fourier, who postulated that Earth's surface temperature is a balance between energy from the Sun ("light rays") and that emitted by Earth ("dark rays"). It was, however, Tyndall who discovered that this balance is determined by the composition of the atmosphere, notably the concentration of CO_2 and aqueous vapor (*1*).

Our capacity to extract subsurface oil for fuel received a boost in 1859 from Edwin L. Drake's success with the first shallow commercial oil well in Titusville, Pennsylvania. Within a few years, portions of the Pennsylvania landscape were dramatically transformed by the proliferation of wells. Although the advent of assembly-line automobile production would not come for another four decades, the spark-ignited internal combustion engine was invented by Lenoir, also in 1859. The combustion of coal, oil, and natural gas worldwide fueled the industrial era, and today global use of these fossil fuels provides about 80% of the energy that we consume to heat buildings, power industries, propel vehicles, and generate electricity. Physical and biological systems in the ocean and on land that remove CO_2 from the atmosphere are unable to absorb or assimilate additional CO_2 at the rate at which it is being produced by the combustion of fossil fuels. More than half of the fossil fuel carbon released by human activities today will remain in the atmosphere for up to a century.

When it comes to the effect of human activities on climate, Svante Arrhenius, a Swedish chemist born in 1859, certainly qualifies as a visionary. He received the Nobel Prize in Chemistry for his theory of electrolytic dissociation, and the mathematical relation that describes the dependence of chemical reactions on temperature—the Arrhenius equation—is named for him. In the 1890s, Arrhenius became interested in the possible effects of the CO_2 released from fossil fuel combustion on Earth's surface temperature. But his interest in this topic arose as he was attempting to calculate how large a change in atmospheric CO_2 concentration would have been required to explain a past cool period of glacial advance during the Pleistocene (*1*). He was aware that many natural processes had influenced Earth's climate on longer time scales. The theory of cyclic glacial episodes had been advanced by Louis Agassiz in the 1840s, and there was a great deal of speculation as to whether a period of intense volcanic activity could, by means of dust clouds, initiate a cool period and give rise to an expansion of glaciers. Another mechanism that could drive the pacing of glacial cycles—variations in the Sun-Earth orbital properties—had been promoted by James Croll and others. Arrhenius began his calculations to examine the plausibility of atmospheric CO_2 concentrations having had a role in these glacial cycles.

Of course, Arrhenius realized that his calculations could work forward as well. In his now-famous work on this topic, he published his estimate that, if releases of fossil fuel emissions were to double the content of CO_2 in the atmosphere, they would cause a globally averaged temperature increase of 5° to 6°C (*2*). For comparison, this is about twice the temperature rise estimated by the Intergovernmental Panel on Climate Change (IPCC) for a doubling of CO_2. Arrhenius, however, could not envision how rapidly an intensely fossil fuel–dependent industrialized society would arise. He estimated that it would take about 3000 years for the atmospheric CO_2 concentration to double (*3*), whereas current IPCC scenarios for the rate of the combustion of fossil fuel and proportion of the CO_2 absorbed by the ocean project a doubling of atmospheric CO_2 concentrations to occur between 2050 and 2080. Although Arrhenius' calculations are occasionally referred to as having been fortuitous "back-of-the-envelope" values, he complained to a friend that it was "unbelievable that so trifling a matter has cost me a full year" (*1*). Critiques of Arrhenius' work by other scientists at the time have been discussed by Weart (*4*).

Further efforts to refine the relationship between anthropogenic release of CO_2 and climate lay largely dormant until the 1930s, when Guy Callendar, a British engineer, took up the problem. Callendar was confident that the warming that had been observed from the late 1800s to the 1930s was attributable to an atmospheric accumulation of fossil fuel emissions, and he predicted an even warmer future if this trend continued (*5*). He may well have been puzzled about the apparent leveling off or downward trend in the Earth's average surface temperature during the 1940s and 1950s. It would be decades later before it could be shown that the anthropogenic release of reflective aerosols, in addition to natural processes, contributed to a slight cooling during this period even though the CO_2 content of the atmosphere was continuing to increase.

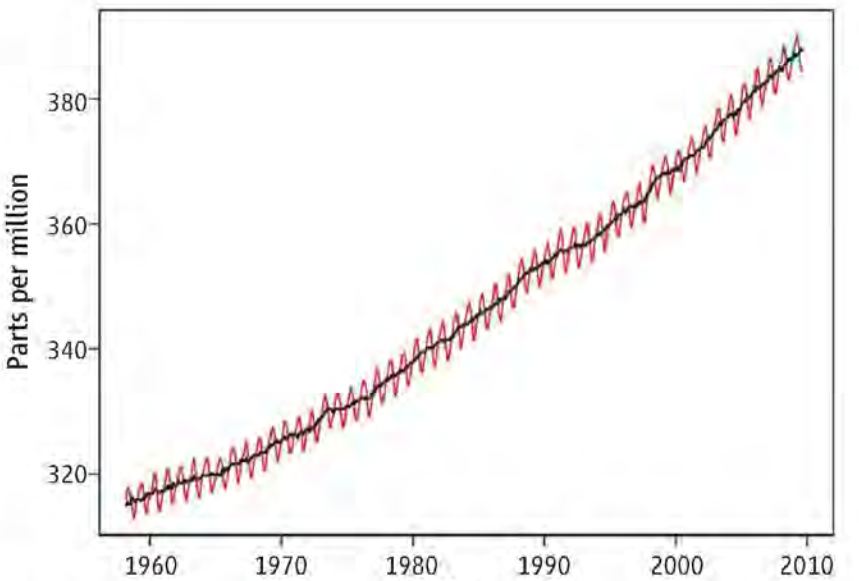


Fig. 1. Keeling curve for atmospheric CO_2. Monthly mean atmospheric CO_2 at Mauna Loa Observatory, Hawaii.

CREDIT: DR. PIETER TANS, NOAA/ESRL

The Past Half-Century: New Observations and Ideas

In 1957, the oceanographer Roger Revelle, expressing concern about the consequences of CO_2 release from fossil fuel combustion, wrote: "[H]uman beings are now carrying out a large scale experiment of a kind that could not have happened in the past nor be reproduced in the future. Within a few centuries we are returning to the atmosphere and oceans the concentrated organic carbon stored in sedimentary rocks over hundreds of millions of years" (*6*). A problem, which any experimental scientist would recognize immediately, is that there is no control against which to compare this experiment—we have only one planet Earth. It would be another couple of decades before we would know how different the atmosphere is on Venus and Mars and come to fully appreciate the role that life processes have played in the evoluton of Earth's atmosphere.

Revelle knew that observing this experiment in the fullest possible way was essential: "This experiment, if adequately documented, may yield a far-reaching insight into the processes determining weather and climate" (*6*). First and foremost, he knew that it was essential to establish precise measurements of the CO_2 content of the atmosphere, and so he recruited a bright young chemist, Charles David Keeling, to develop the analysis and begin these measurements on island locations distant from intense local anthropogenic sources of CO_2. A graph of the continuous record of measurements for CO_2 from 1958 to the present is now widely known as the "Keeling curve." It shows the rhythm of seasonal cycles in terrestrial photosynthesis and respiration, with an average upward slope that has more than doubled, from <1 part per million by volume (ppmv)/year to >2 ppmv/year over the five decades of observation (Fig. 1). Because of rapid interhemispheric exchange, the annual average atmospheric CO_2 concentration at locations away from intense local sources of CO_2 is nearly constant, regardless of latitude.

Agassiz's conclusion that cyclical glacial events had occurred across North America and northern Eurasia needed a mechanism to explain it. Although past episodes of volcanism had been suggested, Croll's orbital theory had the potential to explain the past and project the future as well. This idea received substantial reinforcement with Milankovitch's calculations early in the 1900s on the frequency and amplitude of three components of Earth-Sun orbital relations (*7*). There was, however, little consensus within the Earth science community regarding the significance of orbital cycles in the pacing of glacial events until the 1970s. In part this is because orbital forcing would yield asymmetric cycles, with long glacial periods interspersed with short interglacial periods, which was counter to the prevailing view within geological sciences of four short ice ages over the Quaternary, with long warm periods between them (*8*). The pioneering work of Emiliani and Broecker interpreting oxygen isotope data in corals and in fossil foraminifera from marine sediments supported the idea of orbital-induced Quaternary climate cycles (*8*). Stronger support then emerged with the publication, by paleoclimatologists Hayes, Shackleton, and Imbrie, of data on oxygen isotopes and abundances of foraminiferra fossils in cores of Indian Ocean sediments (*9*). For many Earth and climate scientsts, this work demonstrated a convincing consistency between cycles in the sediment record and Milankovitch calculations of the climatological effects of cycles in Sun-Earth orbital relationships.

At about the same time, public and scientific conceptualizations of "our" Earth were profoundly altered by the first views of Earth from space. Three images of Earth from space remain particularly powerful decades after they were first released: the photograph known as "Earthrise," photographed by Apollo 8 astronaut William Anders on 24 December 1968; the photograph referred to as "The Blue Marble," taken by the crew of Apollo 17 on 7 December 1972; and variations of "Earth at Night."

The Earthrise photograph was taken with a handheld camera as astronauts for the first

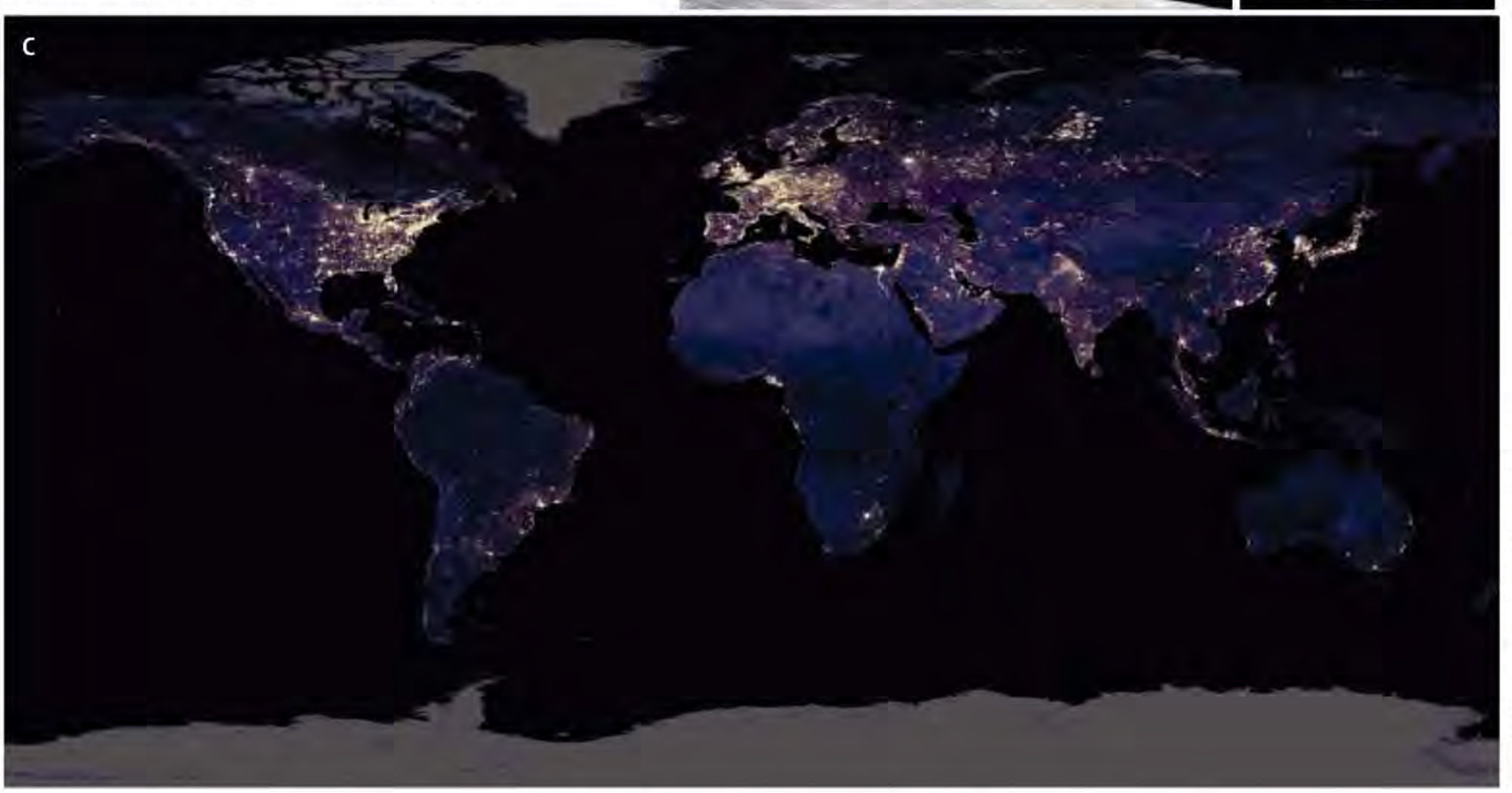


Fig. 2. (**A**) Earthrise (24 December 1968). Image of the rising Earth taken from the Apollo 8 spacecraft. (**B**) Earth taken on 7 December 1972 by the crew of the Apollo 17 spacecraft at a distance of about 29,000 km. This is the first time that the Apollo trajectory made it possible to photograph the south polar ice cap. (**C**) Earth's cities at night. This image of Earth's city lights at night shows the spatial distribution or arrangement of settlements. White areas of light show organized areas where population is typically large.

CREDITS: (A) NASA; (B) NASA, CREW APOLLO 17; (C) NASA

time orbited the Moon and photographed Earth from space. As the path of the spacecraft rounded the Moon and pointed back toward Earth, the planet appeared to rise above the lunar surface and hence the name given to this photograph. Anders' profound reflection on this experience is widely quoted: "We came all this way to explore the Moon, and the most important thing is that we discovered the Earth" (*10*) (Fig. 2A).

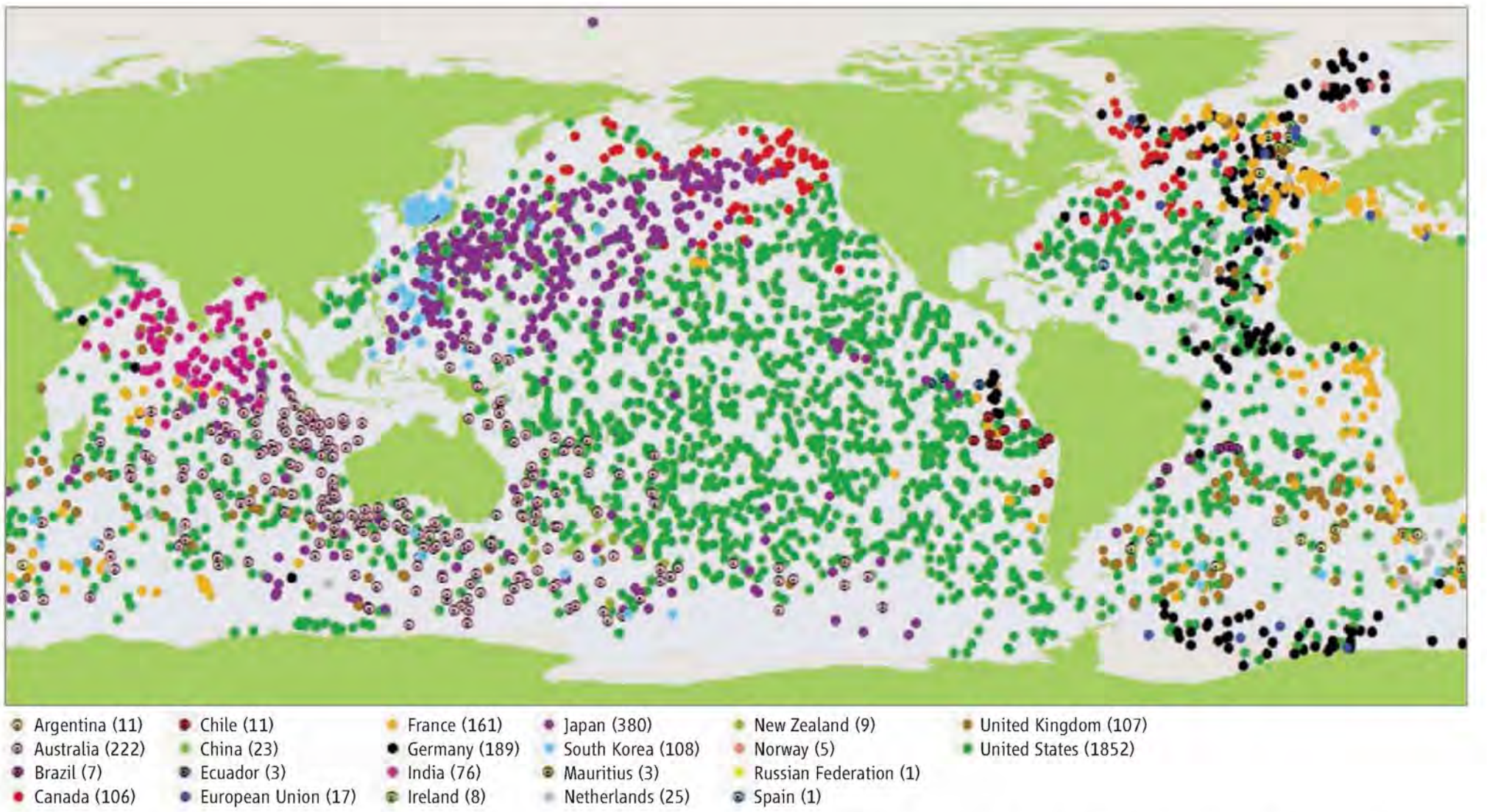
The Blue Marble photograph, sometimes referred to as the most widely reproduced image of Earth, was taken on the last lunar mission. It was, though, the first time that astronauts, who were at the time orbiting Earth to position for their lunar trajectory, saw Earth fully illuminated by the Sun from behind them. Because this launch occurred close to the summer solstice, most of the Antarctic ice cap is visible (Fig. 2B).

Jasanoff (*11*) has written about the power of the Earthrise and Blue Marble images to alter perceptions of our planet's vulnerability. For the most part, national boundaries are invisible in these images, and consciousness of collective human responsibility for the future of our planet is aroused by them. She compares the contrasting perspectives evoked by the image of a well-engineered "Spaceship Earth," a phrase coined by Buckminster Fuller, and that of a fragile craft at risk, as envisioned by Rene Dubos. In analyzing the iconic power of these images, Jasanoff also remarks that they "set up an unresolved dialectic between those who wish to approach environmental problems on a global scale, with gaze averted from the particularities of culture and place, and those who believe that the work of saving the planet must begin with more down-to-Earth considerations, in the realities of lived experience, with questions about the kinds of lives people want to forge for themselves, their communities, and their descendants" [(*11*), p. 49].

The Earth-at-Night images have been produced in a variety of forms to convey different information. Currently they are a product of data collected by a Defense Meteorological Satellite Program–Operational Linescan System (DMSP-OLS) satellite in a near-polar Sun-synchronous orbit. This system was designed to observe clouds by moonlight, but when integrated over an annual cycle, the data can be used to document globally the distributions of various sources of illumination across land and sea. Natural light such as the aurora borealis and aurora australis, lightning and fires started by lightning, reflected moonlight, and clouds are all regularly documented. Images showing oil field gas flares, illuminated squid fishing fleets, and tropical forest burns, though, are dramatic evidence of local human activities. Transient components of these light sources can be filtered to leave geographically fixed sources such as cities, industries, highways, etc. The near-continuum of the illuminated metropolitan areas of Boston, New York, and Washington creates an image of intense human presence, not simply in population numbers but in affluent life-style, particularly when contrasted with comparably populated areas in many other regions (Fig. 2C).

Several astronauts were accomplished Earth scientists before their spaceflights. One of great distinction, Piers Sellers, has remarked, "Apart from letting humanity see Earth differently than ever before, the view from space has also expanded our understanding of how the planet works, and just in time to grasp the impact humanity is having on the planet and its climate system. For the first time, we see our planet as a whole, a system of intricately connected parts that interact—and can be perturbed—in ways humans had not previously glimpsed" (*12*).

Jasanoff (*11*) has also suggested that these images stimulate systematic thinking about Earth's features. Certain features of Earth have now become observable in totality and,



CREDIT: ARGO INFORMATION CENTRE

Fig. 3. Argo floats. The 3325 Argo drifting buoys shown by country of origin for measuring ocean properties deployed across the oceans in February 2009.

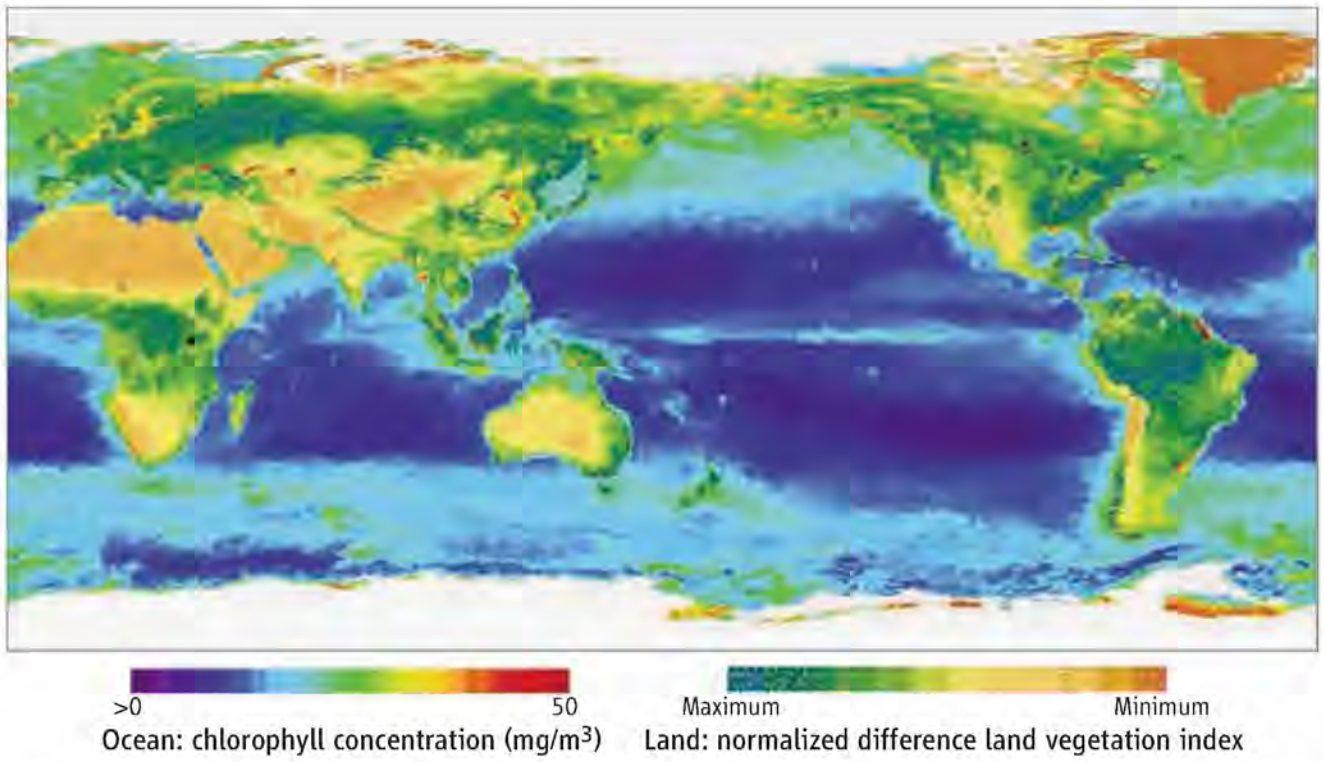


Fig. 4. Global biosphere. Derived weekly maps of surface-ocean chlorophyll distributions from September 1997 to June 1998 reveal dynamic seasonal patterns in primary production during the 1997–1998 El Niño.

more important, interacting scales of the Earth system can now be comprehended that previously were the subject of speculation or at best approximated crudely. The first two images invoke a sense of beauty and perhaps fragility, but they offer little potential for substantive quantitative scientific inquiry. The third image, which can be as awe-inspiring, can clearly be used to document the spatial extent and intensity of certain human activities and to chronicle their changes over time.

Over the past three decades, a broad array of Earth-orbiting satellite sensors and systems have evolved from proof of concept to operational missions and have totally transformed research approaches in many branches of the atmospheric, oceanic, and ecological sciences. An early taste of this new capability came with the launch of SEASAT in 1978. Although a premature circuit failure allowed only a few months of operation, the potential realized with this mission for measuring variation in ocean surface height, wind speed and direction, sea surface temperature, cloud distributions, and polar ice conditions was in many regards as breathtaking for scientists as any prior image of Earth from space. Satellite sensors and systems now provide observational capabilities across the Earth sciences with entirely new dimensions. Today we have geographic continuity in data that was unimaginable a generation ago. Satellite systems are also in many cases both effective complements to and enhanced by in situ land and ocean observations. Observing physical, chemical, and biological ocean properties, for example, involves vast arrays of surface and subsurface drifting buoys. Argo drifting buoys, for example, profile the upper 2000 m of the ocean every 10 days. At the time of the annual meeting (February 2009), 3325 of these were deployed across the global ocean. More than half of the buoys were supported by the United States, but 22 nations participate in this program (Fig. 3).

Many patterns and features in the ocean's physical and biological characteristics have been revealed with these new technologies. Manifestations of interannual climate cycles, such as the El Niño–Southern Oscillation, can now be documented across marine and terrestrial realms as synchronous changes in the intensity of equatorial ocean upwelling, the locations of atmospheric convection, sea level, and the occurrence of precipitation across continents. Images that show the distribution and intensity of ocean and land biomass are compelling examples of such capabilities (Fig. 4).

Continuity in these data sets for land and ocean properties and processes has now become essential in weather forecasting, hurricane warning, management of agriculture, and forestry. These data sets are, in addition, absolutely essential for documenting global climate change such as land surface and ocean surface temperatures, deforestation and other land-use changes, Arctic ice extent, sea-level rise, etc., and for anticipating the impacts of these changes on natural and socioeconomic systems. The precision with which sea-level rise has been measured since the early 1990s with satellite altimeters is vastly superior to earlier data from tide gauges. A downward trend in summer sea ice for the entire Arctic can be documented from the 1950s, but over the past three decades these observations have become far more precise with satellite data. Furthermore, the precision with which cloud cover and winds over the Arctic Ocean and the thickness of sea ice can now be determined with satellite data makes it possible to interpret causes of interannual variation in sea ice extent and volume.

Ironically, as assessments of climate change science and climate impacts have increasingly called attention to changes in climate and documented impacts that were not evident even a half decade earlier (*13–15*), the Earth-observing systems on which advances in this science depend are woefully underfunded. Budgets to develop, deploy, and operate these systems and to support the scientific use of the data have not grown in proportion to the widely recognized need for these capabilities. Worse, domestic funding to sustain them has actually declined over the past decade, even though the United States pioneered many of these systems. Some of the systems now at risk are international partnerships with U.S. funding requirements.

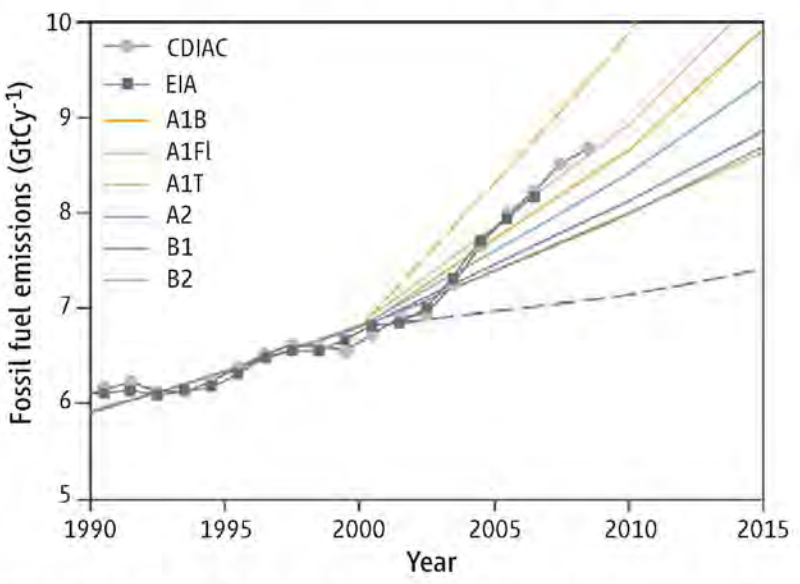


Fig. 5. Actual CO_2 emissions versus IPCC scenarios. Observed global CO_2 emissions from both the Energy Information Adminstration and global Carbon Dioxide Information Analysis Center data, compared with emissions scenarios and stabilization trajectories.

Several organizations have been rising to the challenge of prioritization and support for the deployment of new satellite sensors and renewal of those essential time-series observations of

CREDITS: (TOP) NASA; (BOTTOM) JOSEP CANADELL, GLOBAL CARBON PROJECT, 2009, BASED ON (52)

atmospheric, oceanic, and terrestrial properties and processes. For example, in 2007 a committee of the National Research Council (NRC) prioritized 17 new Earth-observation missions for the 2010–2020 time period out of more than 100 that were proposed. A few months later, the AAAS Board issued a Board Statement on the "Crisis in Earth Observation from Space." It stated that the NRC had provided the "blueprint for a program that will bring immense returns for modest costs" and urged the Congress and the Administration to implement this plan.

The decline in funding for Earth observations has in part been a consequence of NASA's refocusing of priorities with a new emphasis on a return mission to the Moon and on to Mars. The outcome of the Obama Administration's review of NASA's mission for the next decade will signal the degree to which the United States is committed to sustaining and enhancing critical Earth observations.

Capacity to leap beyond the rudimentary calculations of Arrhenius and to use the vast outpouring of data from satellites and other monitoring technologies originated with the development of code to run computer-based climate models. Manabe, Bryan, and Wetherald were pioneers in the application of this approach to climate scenarios with three-dimensional coupled atmosphere-ocean models. Manabe and Wetherald (*16*) provided the first model results run with twice the preindustrial concentration of atmospheric CO_2, which yielded an increased average global temperature of 2°C. Though primitive by today's standards, with, for example, a noninteractive ocean, even early models pointed to enhanced high-latitude warming and an intensified hydrological cycle in a warmer world (*8*). Concerted efforts at many climate modeling centers during the 1980s and 1990s led to improved realism and increased spatial resolution of climate models with the inclusion of cloud physics, interactive oceans, atmospheric aerosols, and interactive vegetation. Over the period of IPCC reports, the geographic and vertical resolution of models have increased about fivefold (*17*).

Many widely used assessments of future climate change and climate impacts have been based on the IPCC Special Report on Emission Scenarios (SRES) (*18*) to generate plausible future climate conditions using several climate models. They portray collective choices that societies make with respect to economic growth, population growth, and options for energy-generating technologies, in addition to their relative emphases on global versus local solutions to economic, social, and environmental sustainability. Thirty-five of these were developed, representing a wide range of demographic, economic, and technological forces that can influence future greenhouse gas and sulfur emissions, and each clustered around one of four storylines for societal development. They explicitly did not include any assumptions regarding implementation of the United Nations Framework Convention on Climate Change or acceptance of the Kyoto Protocol emissions targets and timetables.

The Northeast Climate Impacts Assessment (*19*) used high and low SRES emission scenarios, as did the recently released State of Knowledge Report of the U.S. Global Change Research Program (*15*). In these instances, it is clear that projected impacts across a wide swath of natural and socioeconomic sectors unfold very differently under low- and high-emission scenarios. Because of the relatively long average atmospheric residence time of these incremental greenhouse gases, the outcomes for high- and low-emission scenarios are similar for the first few decades, but beyond that they diverge distinctly. Although this might seem like an obvious outcome, it stands as a powerful statement that in order to diminish the probability of costly impacts decades from now, action must be taken today.

Arrhenius envisioned the prospect of globally warmer conditions having positive local benefits, such as longer growing seasons at high latitudes. As of the 2001 IPCC report, however, it has been evident that negative climate impacts are already in play across the globe. Moreover, it is now well established that the preponderance of projections for impacts above 450 to 550 ppmv of CO_2 are largely negative.

In the 1983 National Academy of Sciences Carbon Dioxide Assessment Committee report, the authors considered the potential for wide-ranging impacts of human-induced climate change, including water availability, agricultural productivity, coastal conditions with sea-level rise, etc., and offered this sobering precaution: "There may yet be surprises … In our calm assessments we may be overlooking things that should alarm us." Indeed, as the past decade of new findings has shown, a warming climate does reveal surprises. To date, most, however, have been unpleasant.

The record of past climate tells us that the transition from one climate state to another is rarely a smooth process. An NRC study (*20*) on abrupt climate change has the ominous subtitle "inevitable surprises." A change in climate can cross a threshold and precipi-

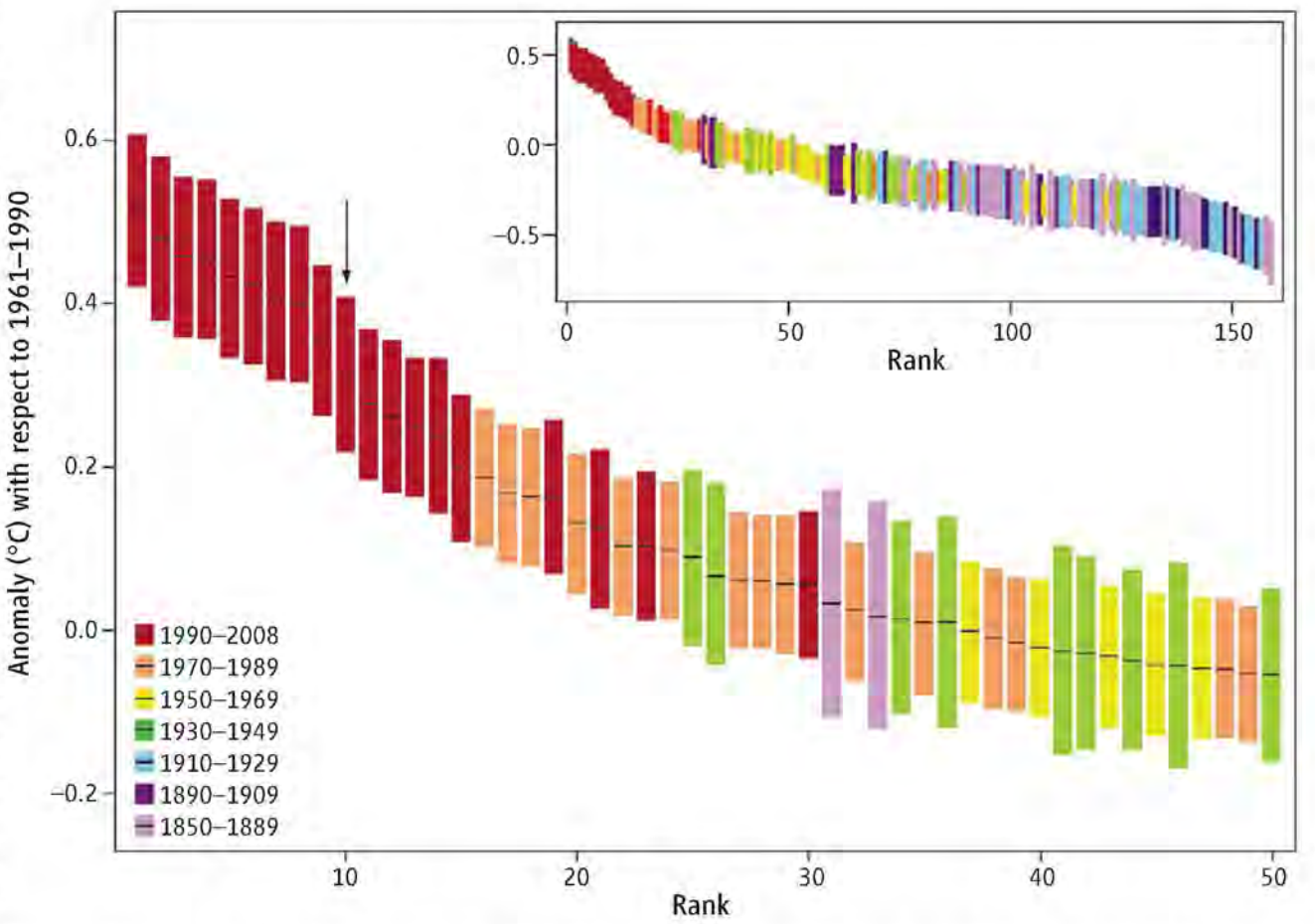


Fig. 6. Global surface temperature. Global ranked surface temperatures for the warmest 50 years. The inset shows global ranked surface temperatures from 1850. The size of the bars indicates the 95% confidence limits associated with each year. The source data are blended land-surface air temperature and sea surface temperature from the HadCRUT3 series. Values are simple area-weighted averages for the whole year (*28*).

CREDIT: MET OFFICE HADLEY CENTRE, UK, AND CLIMATIC RESEARCH UNIT, UNIVERSITY OF EAST ANGLIA, UK; WORLD METEOROLOGICAL ORGANIZATION

tate a change in some other aspect of the system that unfolds more rapidly than the rate of change in the causative agent. An example is the unanticipated collapse of Larsen Ice Shelf B on the Antarctic Peninsula in 2002. In a period of about 1 month, an ice shelf 200 m thick disintegrated, releasing a 700 km^3 volume of icebergs to the sea. It is thought from sediment records that this ice shelf had been stable since the Last Glacial Maximum. Another involving biological systems is the enhanced success of bark beetles with warmer winter temperatures and dry summer conditions that favor the beetle's survival and diminish trees' defense systems. The result may be the massive death of trees across millions of hectacres of forest within only a few years, as with the 1990s spruce bark beetle infestation on the Kenai Peninsula.

Several recent scientific papers and reports have addressed tipping points. Lenton *et al.* (*21*) broaden this concept by defining tipping elements as subsystems of the Earth system that are at least subcontinental in scale and can be switched, under certain circumstances, into a qualitatively different state by small perturbations. The authors take into consideration equilibrium properties, threshold behavior, and critical rates of forcing, and suggest how this analysis can be of policy relevance in decision-making. A range of adverse impacts of abrupt climate change can be compared to develop cautionary strategies via a forewarning system.

A recent National Science Foundation (NSF) report, *Transitions and Tipping Points in Complex Environmental Systems*, addresses these issues across the domains of research, education, and decision-making processes. It argues that NSF should give high priority to interdisciplinary research that focuses on complex environmental systems in order to provide a stronger foundation for informing policy decisions relating to global environmental issues (*22*).

Over the past two decades, many of the future climate projections from the IPCC and other groups have been proven to be conservative. This is in part because an IPCC assessment is by its very nature highly conservative. The content of an IPCC assessment is based on peer-reviewed publications in scientific journals. Thus, the most recent findings, perhaps already widely known among experts, may not be included in an assessment report if the work has not been published. Furthermore, recently published findings that have yet to be corroborated by other investigators may receive less emphasis than well-established work from an earlier period. At times the IPCC assessments have been mischaracterized as extreme exaggerations. A U.S. senator, for example, in a 2001 U.S. Senate hearing, stated that the IPCC summaries for policy-maker documents "tend to take very alarmist viewpoints ... they aren't science, they're UN politics." Responses to such mischaracterizations of IPCC reports describe how the IPCC procedures are faithful to the science and how consistency among the summary statements and the thoroughly documented underlying reports of the working groups is ensured (*23*–*25*).

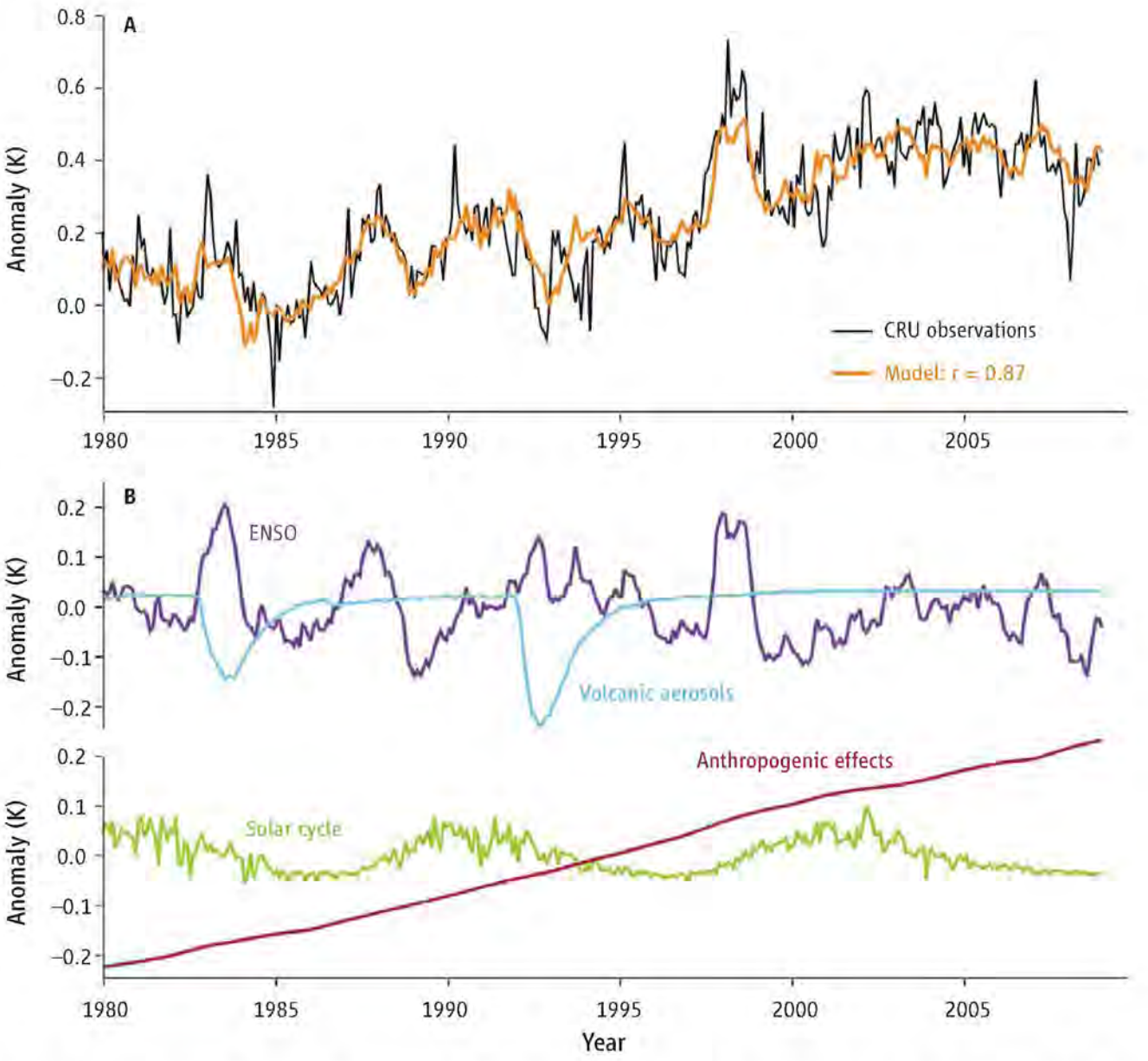


Fig. 7. Reconstructing Earth's recent climate. (**A**) Observed monthly mean global temperatures (black) and an empirical model (orange) that combines four different influences. (**B**) Individual contributions of these influences, namely El Niño–Southern Oscillation (purple), volcanic aerosols (blue), solar irradiance (green), and anthropogenic effects (red). Together the four influences explain 76% (r^2) of the variance in the global temperature observations.

Unfortunately, when data confirm that projections for future climate have been overly conservative, this implies more serious negative impacts. Some aspect of the projected rates for greenhouse gas emissions or for the modeled climate response to these emissions has been underestimated. Greenhouse gas emission data summarized (*26*) and recently updated (Fig. 5) indicate that since 2005, the global annual CO_2 emission rate has been at or above the highest rates projected only 5 years earlier with the set of IPCC SRES marker scenarios. The annual rate of increase in 2007 was 20% higher than the rate of increase one decade earlier. This growth in emissions has largely been due to the fact that rapid economic development in China has been highly dependent on coal. China has now passed the United States as the nation with the highest CO_2 emissions. Fossil fuel emission rates are also growing in India but are currently only about one-fifth those of China. Land-use changes, especially deforestation in tropical nations, now account for about 15% of the global CO_2 emission total of >10 Pg of carbon per year (*27*). This change in land use is consistent with a carbon cycle that is generating stronger climate forcing sooner than expected. Preliminary data for 2009 indicate, however, that the global economic downturn is being reflected in lower CO_2 emissions.

Although 1998 still stands as the warmest year in recent climate history, the 11 warm-

est years in the instrumental record have occurred in the past 12 years. According to the UK Met Office Hadley Centre, 2008 was the 10th warmest year (Fig. 6) [the 8th warmest according to the National Oceanic and Atmospheric Administration (NOAA)]. Late in 2007 and early in 2008, many regions were anomalously cool relative to the past decade, which was consistent with the development of a moderate-to-strong La Niña, and this helps to explain the ranking of 2008 (*28*). Small wobbles in the otherwise steady increase in global temperature over the past two decades are highly consistent with the global climate signal associated with El Niño and La Niña events, volcanoes, and solar variability, superimposed on the warming due to the secular increase in atmospheric greenhouse gas concentrations (*29*) (Fig. 7).

In 2001, the IPCC could not identify any body of science that pointed to a likelihood of a large reduction in Greenland ice during the present century (*30*). Since then, several major outlet glaciers for the Greenland ice cap have shown changes. The termini of many are retreating and thinning at unusual rates, and the increasing frequency of "icequake" seismic events that are spatially coincident with exit glaciers indicates that an acceleration of ice loss is now under way (*31*). Laser altimetry studies demonstrate that extensive dynamic thinning is occurring for glaciers at all latitudes on Greenland, with the most profound changes at the ocean margins (*32*). An abnormally cold 2007–2008 winter across the southern half of Greenland was more than offset by a record-setting summer with an intense melt season, and thus the mass of Greenland ice proceeds along its recent downward trajectory (*33*). Records of numbers of summer melting days continue to be broken (*34*). The trend in the total area of melt during 1979–2008 is approximately +15,900 km^2 $year^{-1}$ and is significant at the 95% confidence interval ($P < 0.01$) (*33*).

Changes are also evident in the rate of sea-level rise. In 2001, the IPCC reported that "[w]ithin present uncertainties, observations and models are both consistent with a lack of significant acceleration of sea level rise during the 20th century" (*35*). But Rahmstorf *et al.* (*36*) have now demonstrated that sea-level rise has accelerated since 1990. The linear IPCC model projections in 1990 gave a best estimate of rise at 2 mm/year. Satellite altimeter data, however, yield an increase of 3.3 ± 0.4 mm/year over the 1993–2006 period. This observed rate of increase is at the upper end of what was projected from the early IPCC scenarios (Fig. 8).

The 2007 IPCC report projected 0.28 to 0.59 m of sea-level rise by 2100. These estimates do not preclude higher rates of rise due to increased rates of ice loss on Greenland and Antarctica. Although the IPCC authors were aware of publications relating to recent changes in Greenland and Antarctic ice balance, they lacked confidence that they could extrapolate meaningfully from these data to future sea-level rise. Rahmstorf (*37*) used a semi-empirical relationship from 20th-century temperature and sea-level changes to project future sea-level rise from the IPCC scenarios for warming and derived an estimate of sea-level rise of 0.5 to 1.4 m for 2100 realative to the 1990 level. When current outlet glacier discharge rates for Greenland are included to improve on the IPCC 2007 projections, Pfeffer *et al.* (*38*) estimated a sea-level rise between 0.8 and 2 m, with a "most likely" estimate being 0.8 m.

A sea-level rise of 0.8 to 2 m over the next nine decades would be of enormous consequence for lives, livelihoods, and property in coastal regions across the globe. Major cities, large portions of nations, indeed entire island nations will become uninhabitable. Add additional tropical storm intensity (*39*, *40*), and damage from any rise in sea level becomes intensified. Recently, the presidents of the island nations of Kiribati and the Maldives have stated that their people must prepare to evacuate (www.sciencenews.org/view/feature/id/40789/title/First_wave). President Anote Tong of Kiribati has promoted training programs to facilitate acceptance of his citizens by other nations.

In 1995, the IPCC was unable to find conclusive evidence that the frequency, intensity, or persistence of extreme weather events had changed. By 2001, however, new data indicated that hot weather had become more extreme and precipitation events more intense in many regions, and that wind and precipitation intensities associated with tropical storms had increased during the latter half of the 20th century. Evidence for these increases is now substantial. Record heat waves across several regions have taken lives and affected agriculture (*41*). The 2007 IPCC projections for weather-related stresses with a warmer climate during the balance of this century include increased incidence of extreme high sea level, increased intensity of tropical cyclone activity, and increased area affected by droughts (likely; >66% probability); increased heavy precipitation events over most areas and increased frequency of warm spells/heat waves over most land areas (very likely; >90% probability); and warmer and more frequent hot days and nights over most land areas (virtually certain; >99% probability) (*42*). In every category of change, adaptive measures will be needed, in some cases urgently and with little advance notice, to minimize loss of life, livelihood, and property as future weather extremes take their toll.

One perplexing aspect of the behavior of the climate system is the degree to which associated changes in biogeochemical cycles and physical aspects of climate tend to amplify rather than mitigate or buffer a change. Albedo feedback in the Arctic is a good example of this. The melting of snow and ice reduces the reflectivity of the surface, and as a result the bare or vegetated land and open water absorb more incident solar energy and warm even more. Rising CO_2 concentrations associated with rising temperatures trigger changes in complex terrestrial ecosystem community dynamics, such as physiological regulation and ecological aspects of water availability.

For example, ecosystems that accumulate carbon under one temperature and CO_2 regime can become a source of CO_2 or methane under another. Boreal terrestrial ecosystems are of central interest in scenarios for a warmer world. Ice core data provide evidence of strong methane feedback responses during periods of warming over the past

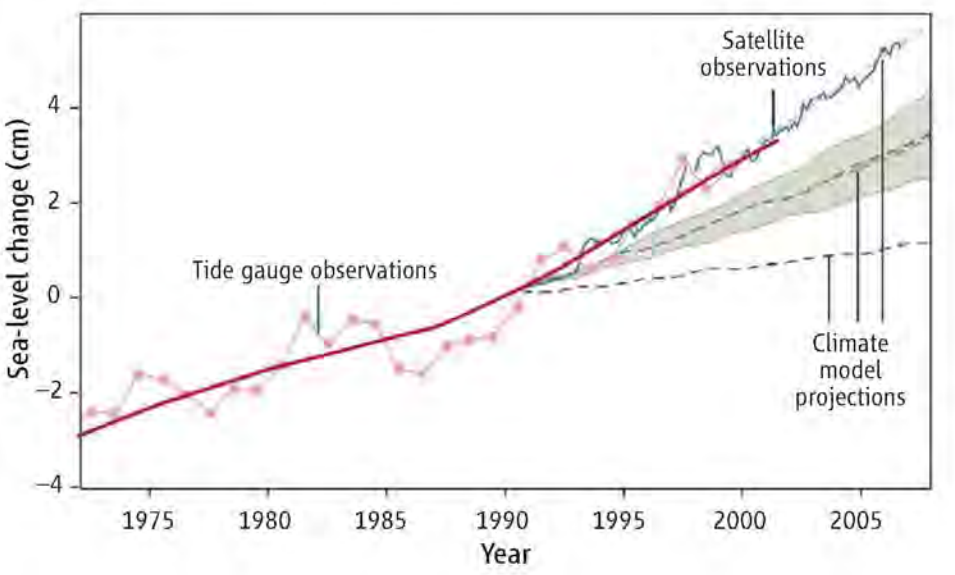


Fig. 8. Sea-level rise. Sea-level data are based primarily on tide gauges (annual, red) and satellite altimeter measurements (3-month data spacing, blue; up to mid-2006) and their trends.

CREDIT: MODIFIED FROM (36)

several glacial cycles, and frozen soils in the Arctic are known to hold substantial reservoirs of methane.

Field studies of lakes formed over melting permafrost suggest that these systems were a major source of methane during past warming periods (*43*). Data from Greenland ice similarly imply that most of the increase in atmospheric methane concentration during the warming immediately after the Younger Dryas (~11,600 years before the present) arose from wetland sources (*44*). Release from seabed methane clathrates has been suggested as another potentially strong positive feedback associated with Arctic warming. The size of this reservoir is estimated at 10^{19} g of carbon, or roughly comparable to the total inventory of coal, oil, and natural gas (*45*). Recent reports of seabed methane releases west of Spitsbergen are hypothesized to be related to warming in this region over the past three decades (*46*). Future releases associated with the warmer climate projected for this century are estimated to be similar in magnitude to the terrestrial biosphere's temperature-amplifying feedback (*47*).

When authors of the 2001 IPCC Working Group II Report looked broadly at the potential for climate change impacts, they found five categories of impacts, which they labeled as "reasons for concern" (RFCs). These included (i) risks to unique and threatened systems (and species); (ii) risks of extreme weather events; (iii) changes that could have positive impacts in some regions and negative ones in others; (iv) changes by which the preponderance of people would be negatively affected; and (v) risks of large-scale discontinuities such as the substantial loss of ice from Greenland or Antarctica, a dramatic increase in the release of methane from frozen ground or seabed sediments, dramatic changes in ocean currents, etc. These RFCs were presented diagrammatically, in what has come to be known as the "burning embers diagram." Some of the same authors and others from the IPCC 2001 assessment recently repeated this analysis and found that compared with the results reported in 2001, smaller increases in global temperature are now estimated to lead to more significant or more substantial consequences in each of the five RFCs. Most dramatic were the changes in the final category (Fig. 9), where surprises with respect to effects of Greenland and Antarctic ice loss on sea-level rise and changes in high-latitude soil carbon dynamics now loom larger than thought likely only a few years ago. Shifts to stronger color intensity in the burning embers diagram suggest, compared to 2001, that we are now drifting even more rapidly toward dangerous interference with the climate system (*48*).

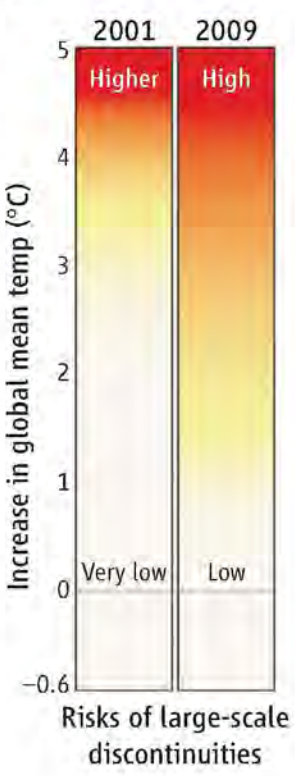


Fig. 9. IPCC RFCs. Increased prospects for low-probability, high-consequence climate impact as assessed in the IPCC Third Assessment (2001) and subsequently (2009) by the same authors. Red (high risk) has moved down to smaller temperature increases since 2001.

Decisions Today Will Determine Which Possible Future Climate Is Realized

In 2007, the IPCC used SRES scenarios to project average global temperature increases for 2001. Mean values for these ranged from 1.8° to 4°C. Each includes assumptions about population, economic development, and dependence on fossil fuels for energy. One of the four SRES marker scenarios has three variants. Each of these assumes the same projections for population, economic development, and societal characteristics, while the fraction of energy needs met with fossil fuels unfolds on three different paths. One is intensively dependent on fossil fuels, rather similar to the current world energy mix; the second represents a strong shift to alternative energy technologies over this century; and the third is an intermediate path. The range for end-of-century warming for these three scenarios, 2.4° to 4°C, indicates the high sensitivity of climate change to the fossil fuel intensity of society's energy systems.

A clear breakthrough in conceptualizing the practicality of dramatic greenhouse gas emission reductions came with the proposal of a stabilization triangle that characterizes the shape of the area of emissions avoided that will be required to stabilize emissions by some future date (*49*) (Fig. 10). Subdividing this triangle into component triangles (wedges) allows one to examine the efficacy and cost-effectiveness of individual efficiencies and technologies against one another. With existing technologies and the commercial-scale adoption of others that can provide energy needed for transportation, industry, domestic needs, etc., with little or no carbon emission, the authors demonstrated that ample resources exist today to begin serious emission reduction.

Beyond the exploration of such a concept in a scientific journal, just how realistic is a proposed transition to a dramatically enhanced future with a decarbonized global energy system? The 2007 IPCC report (*13*) has considered various strategies for this and their associated costs. They reviewed the history of greenhouse gas emission growth since 1970 and explored prospects for emission reductions with existing and likely future technologies, looking at energy supply, transport, buildings, industry, agriculture, forestry, and waste management. They considered the full range of technologies and practices currently available and the potential of those that are projected to be available before 2030. These analyses demonstrate that there is substantial economic potential for the mitigation of global emissions that could reduce the projected growth of emissions. They further found that mitigation opportunities with net negative costs have the potential to reduce emissions by around 6 gigatons (Gt) of CO_2 equivalent $year^{-1}$ in 2030.

The global economic downturn that began in 2008 has slowed the rate of energy use. It is expected that 2009 will be the first year since 1981 to have significantly lower energy use than the prior year, by perhaps as much as 3% (*50*). Projected economic recovery, however, points to the resumption of an upward trajectory in energy use by 2010, with an overall growth of 40% in 2030 relative to 2007, with non–Organisation for Economic Co-operation and Development countries accounting for 90% of this. Projected business-as-usual growth in coal combustion exceeds that for oil and gas.

The International Energy Agency (IEA) also projects the mix of fuels and associated investments that would be required to attain atmospheric stabilization at 450 ppmv of CO_2. This scenario requires that peak emissions be reached before 2020, with end-use efficiency accounting for two-thirds of the early reductions in CO_2 emissions. By 2030, it is projected that emissions can be reduced relative to 2009 by phasing in more efficient coal- and gas-fired power plants (5%), increased dependence on renewables (20%), the use of biofuels for transportation (35%), augmented nuclear power (10%), and carbon capture and storage (10%).

In stating that "[c]ontinuing on today's energy path, without any change in govern-

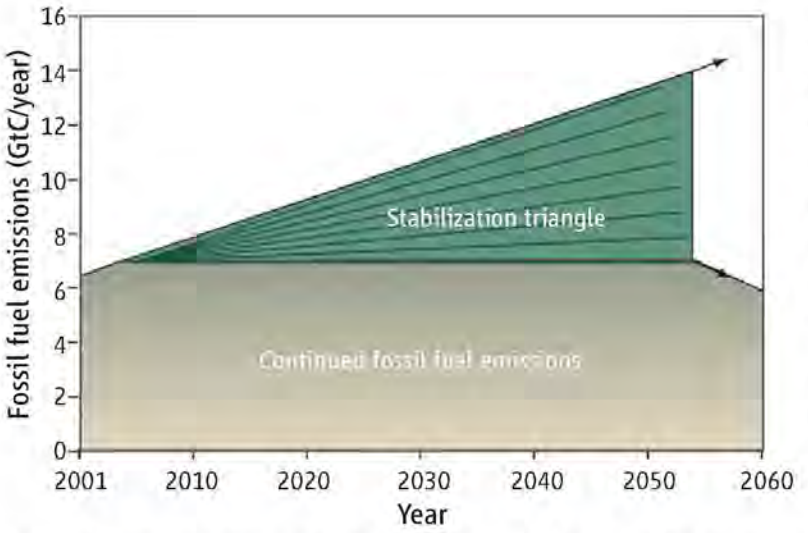


Fig. 10. A path toward stabilization of CO_2 emissions. A stabilization triangle of avoided emissions (green) and allowed emissions (blue) is shown. The allowed emissions are fixed at 7 Gt of carbon year^{-1}, beginning in 2004. The stabilization triangle is divided into seven wedges, each of which reaches 1 Gt of carbon year^{-1} in 2054. With linear growth, the total avoided emissions per wedge is 25 Gt of carbon, and the total area of the stabilization triangle is 175 Gt of carbon. The arrow at the bottom right of the stabilization triangle points downward to emphasize that fossil fuel emissions must decline substantially below 7 Gt of carbon year^{-1} after 2054 to achieve stabilization at 500 ppm.

ment policy, would mean rapidly increasing dependence on fossil fuels, with alarming consequences for climate change and energy security," and "[w]ith a new international climate policy agreement, a comprehensive and rapid transformation in the way we produce, transport and use energy—a veritable low-carbon revolution—could put the world onto this 450-ppm trajectory," the IEA is effectively endorsing the practicality of a dramatic decarbonization of our global energy system. Aggressive research and development to enhance efficiencies, to improve and implement renewable energy technologies, and to avoid releases of greenhouse gases will be required. Within the United States, the Obama Administration's American Recovery and Reinvestment Act is an excellent start. It provides the largest boost in history in federal support for research, development, demonstration, and deployment of clean and efficient energy technologies.

As national governments work toward a stable future climate, the scientific community that has revealed the causes of current and probable future shifts in climate and projected plausible consequences of this trajectory still has serious work to do. Cooperative efforts begun in the 1980s to bridge gaps among the Earth and life sciences in order to address interrelated components of the Earth system have led to much of the understanding that is represented in the IPCC assessments. Further advances in these areas need to be encouraged, and enhanced with closer partnerships with engineering and social science communities. The charter of the Earth System Science Partnership reflects a substantial step in this direction (*51*). Its initiatives relating to the carbon cycle, food security, water, and human health in the context of global environmental change will provide essential new understanding as society steers to a future that diminishes risk for future human well-being and life all across our planet.

In the past year, we have seen the new U.S. administration place scientists of the highest caliber in key positions as advisors and heads of departments and agencies that oversee the pursuit and application of science and technology in this country. We see encouraging indications that much of what is needed in the way of a new spirit of global cooperation in addressing societal problems is being pursued. Never before have scientists been so influential in their active support of sound government policies, nor as selfless in accepting positions of great responsibility in the governance of our nation. It is a moment of pride for the AAAS as we see how many of these scientists have been engaged with our organization throughout their careers. Our most important work, to "advance science, engineering, and innovation throughout the world for the benefit of all people" continues with a new spirit of confident optimism.

CREDIT: MODIFIED FROM (49)

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INTERNATIONAL

Mission to Cuba Yields Hope for Expanded S&T Collaboration

With increasing high-level interest in easing tensions between the United States and Cuba, AAAS President Peter Agre led a delegation to the Caribbean nation for meetings aimed at building a foundation for expanded science and engineering cooperation in the years ahead.

During the three-day visit, the Cubans and Americans agreed to explore areas in which both science and the public interest may be served by bilateral collaboration. In a series of interviews, members of the U.S. delegation identified several fields where the two nations might expand existing efforts or start new initiatives—from meteorology and marine sciences to infectious diseases and informal science education.

"This is one of these key events where you say it's one small step forward, and a long journey lies ahead," said Agre, a Nobel laureate in chemistry. "There's a lot of political debate here in the United States—we very much tried to stay out of the politics.... It was really just about the science."

"Cuba takes so much pride in its science and medical capacities," added Maxmillian Angerholzer III, executive director of the Richard Lounsbery Foundation. "When you're trying to use science as a way to bring countries together, it's best to do it when there are similar interests and shared goals."

The visit, 10–13 November, brought together nongovernmental science and diplomacy leaders from the United States with science leaders from Cuban institutes and universities and staff from the influential Cuban Council of State. In addition, the U.S. delegation met with representatives of a number of foreign embassies and offices based in Havana, as well as the head of the U.S. interests section in Cuba. The delegation's visit was funded by the Lounsbery Foundation.

The trip came at a time of growing interest in scientific engagement between the two neighbors. In October 2008, an editorial in *Science* by Sergio Jorge Pastrana, foreign secretary of the Academia de Ciencias de Cuba, and Michael T. Clegg, foreign secretary of the U.S. National Academy of Sciences, called for both nations to take actions to encourage expanded scientific and engineering relationships. President Barack Obama last spring moved to allow the freer flow of information and humanitarian aid to Cuba, and members of the U.S. Congress are looking at easing or ending the travel ban to the nation.

Delegation member Patrick C. Doherty, director of the U.S.-Cuba Policy Initiative for the New America Foundation, said the current effort at science and technology (S&T) engagement is only the third since the 1960s. In 1997, while president of AAAS, environmental microbiologist Rita Colwell led a three-person delegation that visited Cuban government and science centers. AAAS's Center for Science Diplomacy played a central role with Doherty in organizing the most recent visit.

Center Director Vaughan Turekian, who also serves as AAAS's chief international officer, said progress toward the meetings was slowed by hurricanes that caused extensive damage across the length of Cuba last fall. But in October, Turekian was in Japan for the annual Science, Technology and Society forum. While there, he met Fidel Ángel Castro Díaz-Balart—Fidel Castro's oldest son—a nuclear physicist and leader in his nation's science policy community.

"I was able to tell him about our planned delegation and the fact that Peter Agre would be leading it," Turekian said. "He was very receptive and helped facilitate a meeting with his own staff when we were in Havana."

Other members of the U.S. delegation were Anthony "Bud" Rock, chief executive officer of the Association of Science and Technology Centers; retired U.S. Army Colonel Lawrence Wilkerson, former chief of staff to U.S. Secretary of State Colin Powell and now professor of government at the College of William and Mary; Anya Landau French, director of research for the U.S.-Cuba Policy Initiative at the New America Foundation; and Steven Clemons, senior fellow and director of the American Strategy Program at the New America Foundation.

Along with talks on research collaboration, Rock said, the delegation also spent "considerable time" discussing how "to make sure the results of that research are put to work for the people."

Agre described "a spark of friendship" that he experienced in a meeting where he sat with Pastrana and Academia de Ciencias President Dr. Ismael Clark Arxer. "We didn't know each other before ... but there was a common bond of science that just broke through," he said.

Still, Agre and others noted the continuing embargo and tension in governmental relations, and they cautioned against raising hopes too quickly for scientific cooperation.

"There's only so much we can do right now," said Angerholzer. "Perhaps what's more important is that we're building bridges that can be utilized in the future. Science and medicine are areas that can be scaled up right away if relations are someday normalized."

Hopeful visit. In top-level meetings at the Havana headquarters of the Academia de Ciencias de Cuba, delegates discussed future scientific cooperative efforts between the two nations.

REGIONAL DIVISIONS

Teachable Moments at AAAS Caribbean Meeting

SAN JUAN, Puerto Rico—On matters of science education and public engagement, Daniel Altschuler is a realist. As a popular author and former director of the Arecibo Observatory, he knows firsthand that even people with scant scientific background are fascinated by the question of life on other planets.

Daniel R. Altschuler

And so, as he stood before an audience that included many young students and their teachers at the annual conference of the AAAS Caribbean Division, Altschuler recognized an opportunity. He opened his talk by surveying the depiction of UFOs and aliens in history and in today's popular culture; then, with his audience hooked, he segued into plain-spoken lessons on cosmology, chemistry, and even mathematics that must guide any scientific effort to explore the realms beyond Earth.

It was a signature moment at the Caribbean Division's annual conference, held 24 October at the Puerto Rico Convention Center. The day-long event featured talks on Darwin, microbes, and the International Year of Astronomy, plus "green chemistry" workshops for students at different levels—but the overarching theme was building public interest in science.

"We strongly believe that the public, including poor and disadvantaged groups, has the right to enjoy the benefits of scientific progress and its applications," said division President Jorge Colón, an associate professor of chemistry at the University of Puerto Rico. "But that right can only be fulfilled if science and technology are broadly available and accessible so that all members of society will appreciate them [and] understand their significance."

Antonio Lazcano

The two headline speakers—Altschuler and Mexican biologist Antonio Lazcano—have strong international credentials.

Lazcano is a professor at the Universidad Nacional Autónoma de México (UNAM) in Mexico City. He has studied the origin and early evolution of life for more than 35 years, and his 1984 book, *El Origen de la Vida* (*The Origin of Life*), has sold more than 600,000 copies. He was the first Latin American scientist to serve as president of the International Society for the Study of the Origin of Life.

Altschuler is the author of *Children of the Stars* (2002), published in Spanish as *Hijos de las Estrellas*. The conference was dedicated to Altschuler for his long work in promoting science at Arecibo, where he led the effort to build a visitors center, and in Puerto Rico and the Caribbean region.

Each scholar, in his talks, drew the connection between the origin of life on Earth and the remarkable story of the universe. And in interviews, each expressed concern that the worldwide recession is reducing resources for science education and public outreach.

Latin America has produced "extraordinary writers, extraordinary painters, extraordinary artists," Lazcano said. "Clearly we have the intellectual capacity to produce extraordinary scientists. But that requires a long-term vision from politicians and from society to demand that the investments—not only economic, but social and political—continue regardless of the changes in regimes or the economy."

Failure to make that investment leaves segments of society cut off from knowledge, and that leaves them vulnerable to the appeal of creationists, Lazcano said.

Altschuler would like to see a major regional science center in Puerto Rico—a museum that could inspire visitors while helping to support science teachers and journalists.

"It's an investment in the future," he said. "If you get one out of 100 kids who visit to pursue a career in science or engineering or math, you begin to get a very real return on your investment."

AAAS ABELSON SERIES

Top Researchers Share Translation Successes

Pioneering efforts to rapidly transfer laboratory insights into clinics, and vice versa, were the focus of the 2009 Abelson Advancing Science event at AAAS.

Two top researchers—Hal Dietz and Erin Lavik—described laboratory insights that have evolved into projects intended to help people with glaucoma, spinal cord injuries, and other diseases rare and common.

Their "gutsy," groundbreaking work exemplifies the approach necessary for speeding medical advances, said event moderator Elias Zerhouni, M.D., chief scientific adviser for *Science Translational Medicine.* The 20 November discussions on "Translational Medicine and Human Health" honored the late Philip Hauge Abelson, a longtime AAAS senior adviser and *Science* editor emeritus.

Too often, Zerhouni said, basic advances have not translated into medical breakthroughs. Work in model systems may not always translate to human-scale problems. Inadequate funding may be another part of the problem: The U.S. biotechnology and pharmaceuticals sectors in 2008 spent more than $60 billion on research and development—an investment roughly twice the size of the budget of the National Institutes of Health (NIH), Zerhouni said.

"There is no magic solution," said Zerhouni, a senior fellow with the Bill & Melinda Gates Foundation and former NIH director. "But we'd better find a solution," given the burden of disease.

Lavik described tiny capsules designed to slowly release protective drops into the eyes of glaucoma patients. Lavik, who holds the Elmer Lindseth Chair of Biomedical Engineeering at Case Western Reserve University, has also combined blood vessel and neural stem cells with a polymer matrix to generate new blood vessels and rebuild the blood–spinal cord barrier of injured animals. Her latest project—using a nanoparticle to activate blood platelets—might someday improve trauma care by slowing the bleeding that exacerbates spinal cord damage after an injury.

"We have to listen to the clinician," Lavik advised fellow researchers. "We can have wonderful conversations about building new technologies and translating those technologies."

Howard Hughes Medical Institute Investigator Dietz, the Victor A. McKusick Professor of Genetics and Medicine at the Johns Hopkins University School of Medicine, began his research on Marfan syndrome out of concern for patients with the rare genetic disease. But he also thought that understanding the disorder, which can cause severe heart defects, might offer insights into more common conditions.

In mice, the blood-pressure medicine losartan blocked the activity of a growth factor, TGFß, and prevented aneurysm. Evidence of similar protection was seen among children with severe Marfan syndrome, resulting in a clinical trial. "To date, we've treated 19 such children," Dietz said. "On average, [they] were growing their aortas by 4 millimeters per year, every year prior to this medication, and only 0.4 millimeters a year after starting losartan."

He also investigated treating mitral valve disease with losartan, and he applied a TGFß blocker to normalize muscle performance in a mouse model of Duchenne muscular dystrophy. In early studies with Enid Neptune, he is trying to block TGFß in common forms of lung disease, including emphysema induced by cigarette-smoke exposure.

Translating promising results to improve human welfare will require "more basic research and greater and more diverse multidisciplinary interactions," Zerhouni said.

—Ginger Pinholster

AAAS Members Elected as Fellows

In November, the AAAS Council elected 531 members as Fellows of AAAS. These individuals will be recognized for their contributions to science and technology at the Fellows Forum to be held on 20 February 2010 during the AAAS Annual Meeting in San Diego. The new Fellows will receive a certificate and a blue and gold rosette as a symbol of their distinguished accomplishments. Presented by section affiliation, they are:

Section on Agriculture, Food, and Renewable Resources

Caitilyn Allen, Univ. of Wisconsin, Madison • Steven R. Archer, Univ. of Arizona • David D. Baltensperger, Texas A&M Univ. • Wilbert H. Blackburn, USDA • Michael D. Casler, USDA • Joseph Chappell, Univ. of Kentucky • Robert Bruce Goldberg, Univ. of California, Los Angeles • Peter K. Hepler, Univ. of Massachusetts, Amherst • Harry J. Klee, Univ. of Florida • Donald P. Knowles, Washington State Univ. • Clint W. Magill, Texas A&M Univ. • Ronald J. Nachman, USDA • Henry T. Nguyen, Univ. of Missouri • Peggy Ozias-Akins, Univ. of Georgia • Ivette Perfecto, Univ. of Michigan • Gary A. Peterson, Colorado State Univ. • Anireddy Reddy, Colorado State Univ. • Robert Schmidt, Univ. of California, San Diego • David Spooner, Univ. of Wisconsin, Madison • Bruce E. Tabashnik, Univ. of Arizona • Ewen Cameron David Todd, Michigan State Univ. • George F. Vance, Univ. of Wyoming • Donald P. Weeks, Univ. of Nebraska, Lincoln • Valerie Moroz Williamson, Univ. of California, Davis • Carol E. Windels, Univ. of Minnesota

Section on Anthropology

Susan M. Cachel, Rutgers Univ. • Diane Zaino Chase, Univ. of Central Florida • Katerina Harvati, Max-Planck Institute for Evolutionary Anthropology. • Andrew Hill, Yale Univ. • Gary D. James, Binghamton Univ., SUNY • Ellen Messer, Brandeis Univ. • Yolanda Moses, Univ. of California, Riverside • Lynnette Leidy Sievert, Univ. of Massachusetts, Amherst

Section on Astronomy

James M. Cordes, Cornell Univ. • Eileen D. Friel, Lowell Observatory • Philip R. Goode, Big Bear Solar Observatory • Alyssa A. Goodman, Harvard Univ. • Christopher Impey, Univ. of Arizona • Mario Livio, Space Telescope Science Institute • Kevin Marvel, American Astronomical Society • Ramesh Narayanan, Harvard-Smithsonian Center for Astrophysics • Patrick S. Osmer, Ohio State Univ. • Lawrence A. Taylor, Univ. of Tennessee, Knoxville • Saeqa Dil Vrtilek, Smithsonian Astrophysical Observatory • David Hal Weinberg, Ohio State Univ.

Section on Atmospheric and Hydrospheric Sciences

Meinrat O. Andreae, Max-Planck Institute for Chemistry • Ronald Benner, Univ. of South Carolina • Mark A. Brzezinski, Univ. of California, Santa Barbara • John W. Farrington, Woods Hole Oceanographic Institution • John E, Kutzbach, Univ. of Wisconsin, Madison • Diane M. McKnight, Univ. of Colorado, Boulder • Jonathan Overpeck, Univ. of Arizona • Joyce E. Penner, Univ. of Michigan • Stephanie L. Pfirman, Barnard College • Philip J. Rasch, Pacific Northwest National Laboratory • Armistead G. Russell, Georgia Institute of Technology

Section on Biological Sciences

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Pictured: *GRC Director Emeritus Alexander M. Cruickshank, current GRC Director Nancy Ryan Gray, and GRC Director Emeritus Carlyle B. Storm*

The David Starr Jordan Prize Committee is pleased to announce the sixth David Starr Jordan Prize Winner:

Dr. Anurag Agrawal

of the Department of Ecology and Evolutionary Biology, Cornell University

Dr. Agrawal is one of the foremost authorities on the community and evolutionary ecology of species interactions. Currently an Associate Professor at Cornell (see www.herbivory.com), Dr. Agrawal was previously Assistant Professor of Botany at the University of Toronto. An undergraduate at the University of Pennsylvania, he received his PhD at the University of California, Davis in 1999. Dr. Agrawal has made highly influential contributions, including empirical and conceptual advances in our understanding of plant defense against herbivory, impacts of genetic diversity on community processes, coevolutionary interactions between monarch butterflies and milkweeds, and deciphering the success of invasive plants. His work has been presented in over 100 papers, has been cited over 3,000 times and has been presented in 75 invited lectures. He currently serves as an Associate Director of Cornell's Center for a Sustainable Future.

In 1986, Cornell, Indiana and Stanford Universities established a joint endowment to fund a prize in honor of David Starr Jordan, a scientist, educator and institution builder of enormous influence on higher education in the United States who had important ties to each of these universities. The prize is international in scope and presented approximately every three years to a young scientist (40 years of age or less) who is making novel innovative contributions in one or more areas of Jordan's interest: evolution, ecology, population and organismal biology. The intent of the David Starr Jordan Prize is to recognize scientists who are making research contributions likely to redirect the principal foci of their fields. The sixth David Starr Jordan Prize carries an award of $20,000.00. In addition to a cash award, Dr. Agrawal will receive a commemorative medal, will attend an award ceremony (this year at Cornell), and visit the other sponsoring institutions to give scholarly presentations of his work.

For more information including a list of previous prize winners and their accomplishments, visit: www.davidstarrjordan.org

Regiodivergent Ring Opening of Chiral Aziridines

Bin Wu, Jon R. Parquette,* T. V. RajanBabu*

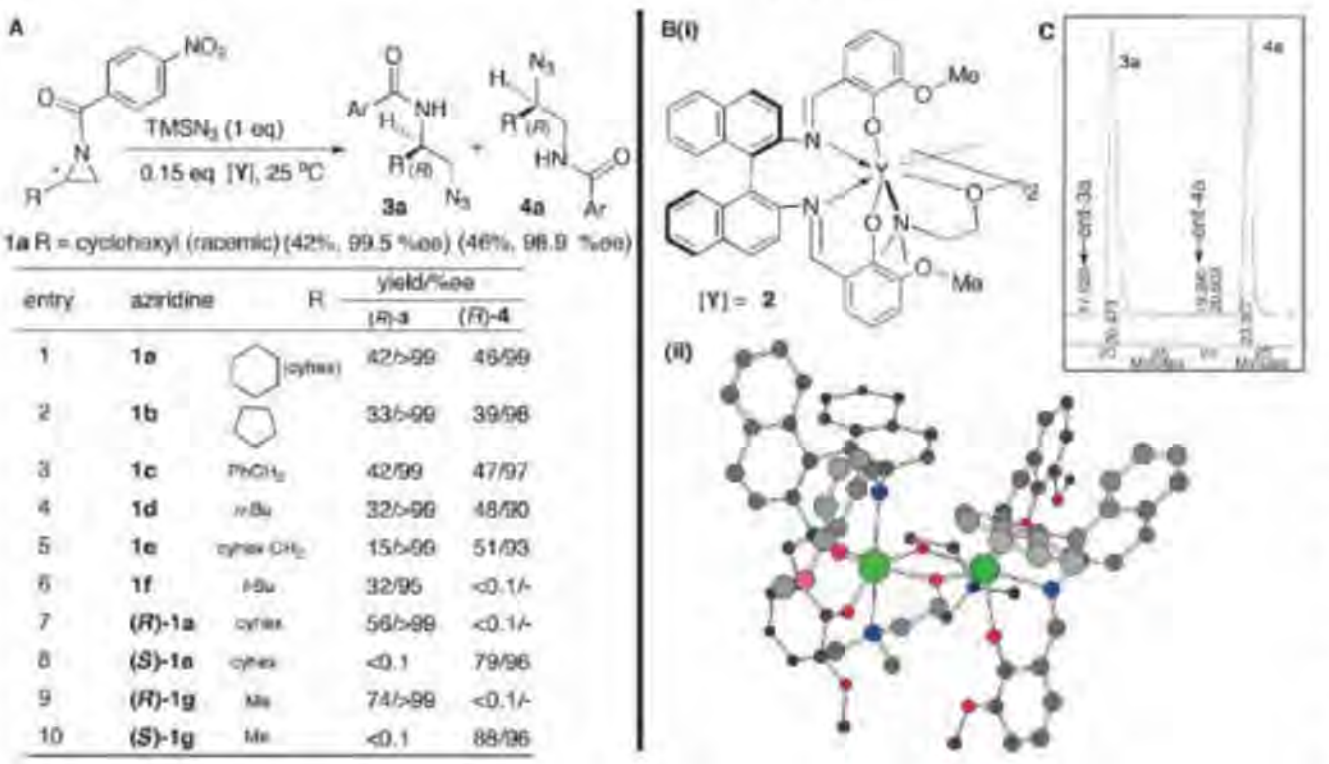
There are two common classes of asymmetric catalysis. In one class, the catalyst preferentially accelerates formation of one enantiomeric product over the other in the reaction of a prochiral reagent. In the second class, the catalyst preferentially accelerates reaction of one enantiomeric reagent over the other, a process termed kinetic resolution (*1*, *2*). Both of these scenarios derive selectivity purely from rate differences associated with a single conserved reaction pathway. In a third, much rarer class, the catalyst accelerates the reaction of both members of a racemic mixture but does so along divergent pathways, inducing opposing chemoselectivity or regioselectivity in its respective encounters with each enantiomeric reagent (*3*). An advantage of this approach is that a full racemic mixture can be transformed into a set of desirable chirally resolved products.

Traditional enantioselective desymmetrizations of meso-epoxides (*4*) and aziridines (*5*), as well as kinetic resolutions of racemic epoxides (*6*), have been established as highly useful processes for the synthesis of enantiopure intermediates. The family of Cr(III)-salen catalysts shows impressive regioselectivities in ring openings, although it does not appear to be at the level of fully discriminating between enantiomers (*7*). The report that comes closest to a regiodivergent reaction scheme for this substrate class is an enzyme-catalyzed ring opening of epoxides (*8*). Even this case, however, relied on the use of two different enzymes in the same reaction mixture, each of which independently catalyzed the reaction of its favored enantiomer. Here, we report that a single chiral small-molecule catalyst (**2**) induces divergent regioselectivities in the ring-opening reactions of racemic aziridine mixtures. High yields of 1,2-diamine derivatives can be obtained in nearly enantiomerically pure form [>97% enantiomeric excess (ee)] from racemic aziridines by this process (Fig. 1A table). The stereospecific nature of the azide attack inverts the configuration of one of the enantiomers. Thus, the configurations of the chiral centers in both β-azidoamides are identical, and it should in principle be possible to convert both compounds into a single 1,2-diamine derivative by subsequent transformations.

In initial experiments, we found that in the presence of trimethylsilylazide ($TMSN_3$) the dimeric yttrium-salen complex **2** (*5*) (Fig. 1B) catalyzed the ring-opening reactions of the two enantiomers of **1a** with exceptionally high, complementary regioselectivities (*9*). Accordingly, the nucleophilic attack occurs at the primary position in (*R*)-**1a**, leading to the azidoamide **3a** as the exclusive product, whereas (*S*)-**1a** gives the product **4a**, resulting from exclusive S_N2-inversion at the secondary center. The ee (54%, *R* major) of the small amount of recovered starting material **1a** suggests that the more-reactive (*S*)-enantiomer is consumed about 3.35 times faster than the slow-reacting (*R*)-isomer. A number of structurally different aziridines were subjected to the ring-opening reactions, and the results are listed in the table. For most substrates (entries 1 through 5, 7, and 9), the reaction proceeds with >99% enantioselectivity in the formation of the primary azide **3**. For the *t*-butyl derivative (entry 6), the selectivity is slightly lower (95% ee). Selectivities in the formation of **4** [mostly from the fast-reacting (*S*)-aziridine] are also impressive, with slightly lower values observed for **1d** (90% ee) and **1e** (93% ee). Curiously, in the case of the *t*-butylaziridine (**1f**), the normally fast-reacting (*S*)-isomer was recovered along with some of the unreacted (*R*)-isomer (entry 6). Apparently, the superior kinetic selection by the catalyst cannot completely overcome the inherent reactivity of this substrate.

The high specificity of the reactions and identity of the products were further confirmed by reactions of enantiopure aziridines with $TMSN_3$ (entries 7 to 10). Even in the exceptionally challenging situation where the enantiomers differ solely by placement of a methyl group (entries 9 and 10), the (*R*)-enantiomer of the aziridine gives exclusively the primary azide (*R*)-**3 g** (>99% ee) and the (*S*)-enantiomer, the secondary azide (*R*)-**4 g** (96% ee), with no trace of contamination by the regioisomeric product in either case.

The exact origin of the selectivity of this catalyst remains to be established. Control experiments [see (*9*)] suggest that both the rate acceleration and selectivity are quite sensitive to the catalyst structure. It is conceivable that the capsular nature of the chiral bimetallic catalyst, as revealed by its solid-state structure, helps to bind the two enantiomers of the aziridine in distinct orientations during the activation process, and each of the diastereomeric complexes has a different electrophilic carbon favorably juxtaposed for attack by the nucleophile, possibly activated by the second yttrium.



entry	aziridine	R	yield/%ee (*R*)-3	(*R*)-4
1	1a	(cyhex)	42/>99	46/99
2	1b		33/>99	39/96
3	1c	$PhCH_2$	42/99	47/97
4	1d	*n*-Bu	32/>99	48/90
5	1e	cyhex CH_2	15/>99	51/93
6	1f	*t*-Bu	32/95	<0.1/-
7	(*R*)-1a	cyhex	56/>99	<0.1/-
8	(*S*)-1a	cyhex	<0.1	79/96
9	(*R*)-1g	Me	74/>99	<0.1/-
10	(*S*)-1g	Me	<0.1	88/96

Fig. 1. (**A**) Regiodivergent kinetic resolution of racemic aziridines. (**B**) (i) Chemical and (ii) solid state [from (*5*)] structure of the dimeric Y catalyst; H atoms omitted for clarity. (**C**) Chiral stationary phase high performance liquid chromatography (HPLC) analysis of reaction products of **1a**.

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Stepwise Modification of a Modular Enhancer Underlies Adaptation in a *Drosophila* Population

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The evolution of cis regulatory elements (enhancers) of developmentally regulated genes plays a large role in the evolution of animal morphology. However, the mutational path of enhancer evolution—the number, origin, effect, and order of mutations that alter enhancer function—has not been elucidated. Here, we localized a suite of substitutions in a modular enhancer of the *ebony* locus responsible for adaptive melanism in a Ugandan *Drosophila* population. We show that at least five mutations with varied effects arose recently from a combination of standing variation and new mutations and combined to create an allele of large phenotypic effect. We underscore how enhancers are distinct macromolecular entities, subject to fundamentally different, and generally more relaxed, functional constraints relative to protein sequences.

Three major challenges for understanding the genetic and molecular bases of morphological evolution are to identify loci underlying trait divergence, to pinpoint functional changes within these loci, and to trace the origin of functional variation in populations. The evolution of animal morphological diversity is generally associated with changes in the spatial expression of genes that govern development (*1*, *2*). The divergence of particular morphological traits has been linked to changes in specific enhancers of individual loci (*3*–*9*). Mutations in individual, modular enhancers are thought to circumvent the potentially pleiotropic effects of mutations in coding sequences of genes that participate in many developmental processes (*10*–*12*).

Nonetheless, there is relatively little detailed knowledge of how enhancer sequences evolve, of the genetic path of enhancer evolution. In most instances, functional mutations have not been identified, so their individual effects and origins have not been traced. In contrast, the evolutionary paths of several proteins have been traced and revealed that many trajectories, including reversals, are not allowed because of structural constraints (*13*–*15*). To decipher the mode and tempo of regulatory sequence evolution, we must determine the following: How many mutations are involved in enhancer divergence? What effects do individual mutations have? And, what is the relative contribution of standing variation and new mutations to enhancer evolution?

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To identify enhancers that have recently evolved, we have traced the recent evolution of adaptive pigmentation within African populations of *Drosophila melanogaster*. We elucidate a specific set of regulatory mutations that underlie changes in gene expression and pigmentation and reconstruct the path of enhancer evolution.

Adaptive melanism in a *Drosophila* population. Across Africa, a strong correlation exists between elevation and the degree of abdominal pigmentation in *D. melanogaster* populations (*16*). This correlation is not explained by population structure, indicating that dark pigmentation is a derived adaptation to high altitude or a correlating selective pressure. Previous study of a dark population from Uganda (*16*) uncovered a partial selective sweep at the *ebony* locus, where the darkest third chromosome lines (Fig. 1) share a 14-kilobase haplotype block of nearly identical sequence extending over the noncoding region of the *ebony* locus (fig. S1). *ebony* encodes a pleiotropic, multifunctional enzyme in the biogenic amine synthesis pathway (*17*) that functions in a variety of processes. In the adult cuticle, expression of *ebony* is required in regions that will generate a yellow shade (*18*), and its absence causes a dark, melanic cuticular phenotype.

The partial sweep at the *ebony* locus and its association with dark pigmentation is evidence that genetic variation at *ebony* contributes to the melanic phenotype (*16*). To test this association directly, we undertook a series of transgenic complementation experiments with use of *ebony* transgenes from light (U62) and dark (U76) extraction lines. In an *ebony* null mutant background, we found that the pigmentation phenotypes of animals bearing the light (U62) and dark (U76) transgenes differed by about 10 pigmentation units (figs. S2A and S3). This is similar to the magnitude of pigmentation difference between the U76 and U62 extraction lines (fig. S2A). Furthermore, in the genetic background of the dark U76 line, we found that a single copy of the light (U62) transgene was sufficient to fully complement the melanic abdominal phenotype (fig. S2B). These results suggest that variation at *ebony* can account for much of the phenotypic variation between extraction lines.

In addition, on the basis of the identification below of haplotypes containing causative mutations, we used a standard analysis of variance approach to estimate the contribution of these haplotypes to phenotypic differences. We found that variation at *ebony* accounts for up to 83% of the total phenotypic variation [supporting online material (SOM) text]. These results confirm that *ebony* is the major locus responsible for the dark phenotype of the Ugandan extraction lines.

Noncoding variation at *ebony* causes abdominal melanism. The association between variation at *ebony* and melanic pigmentation could be due to divergence in the regulation of *ebony* expression and/or protein function. However, among the light and dark transgenes tested, the dark allele contained no derived coding differences relative to the species consensus (fig. S4), and only one derived difference existed in the light U62 line (P46T), suggesting that causative changes lie outside the coding region. To test whether a transcriptional regulatory difference may be responsible for the dark pheno-

Fig. 1. Variation in abdominal pigmentation within a Ugandan population of *D. melanogaster*. Each abdomen is derived from an extraction line bearing a homozygous third chromosome from a Ugandan population sample. The name of each line designates the percent darkness of the A4 abdominal tergite. *ebony*^{AFA} is a null mutation.

type, *ebony* mRNA expression in newly eclosed adults was visualized by in situ hybridization (Fig. 2). There was a marked reduction (58 to 83%) in *ebony* mRNA expression in darker lines (Fig. 2 and table S1). The association of the dark phenotype and haplotype with decreased *ebony* mRNA suggests that cis regulatory sequence mutations have accumulated that reduce *ebony* expression.

To localize regions of the *ebony* locus responsible for the dark phenotype, we tested the activity of chimeric *ebony* transgenes in which the upstream regulatory region of each allele was fused to the downstream first exon and coding region of the other allele. The light/dark construct performed nearly as well as the light construct in complementing the abdominal phenotype of an *ebony* null mutant (Fig. 3, C and G), whereas the reciprocal dark/light transgene yielded a phenotype similar to that of the complete dark allele construct (Fig. 3, D and G). The phenotypes of the chimeric transgenes indicate that the functional differences between the light and dark alleles largely reside in the 5′ noncoding region of the locus, presumably within enhancers.

Regulatory divergence at ebony is restricted to a modular enhancer. To identify enhancers within the *ebony* regulatory region (figs. S5 and S6), we fused fragments of noncoding DNA to a green fluorescent protein (GFP) reporter gene and monitored reporter expression in adult tissues. We identified an array of modular enhancers with activities in many tissues that exhibit *ebony* mutant phenotypes or that express the gene (Fig. 4A and fig. S5). One enhancer active in the developing abdomen (and thorax) was localized to a 0.7-kb fragment located 3.6 kb upstream of the *ebony* promoter ("abd" in Fig. 4A). The abdominal element drove reporter expression in a broader domain than that of the native *ebony* expression pattern, including the posterior regions of each tergite (fig. S6H) and the male A5 and A6 segments (fig. S6, E and F). However, the extension of reporter constructs to include promoter-proximal and intronic sequences resulted in a precise recapitulation of the endogenous *ebony* expression pattern (fig. S6, N and T).

Regulatory mutations are suggested to minimize pleiotropic effects relative to coding mutations because of the modular organization of cis regulatory regions (*10*–*12*). However, the modularity of enhancers has not yet been tested with naturally occurring mutations in a comprehensively defined regulatory region. To examine whether regulatory mutations in one module impact the function of adjacent modules, we generated GFP reporter constructs bearing the upstream region fused to the first introns from both light (U53) and dark (U76) alleles and measured reporter protein activity in various tissues (Fig. 4 and fig. S7). In the developing head (Fig. 4, B and C), legs (Fig. 4, D and E), larval brain (Fig. 4, F and G), wing (Fig. 4, H and I), and haltere (Fig. 4, J and K), both light and dark regulatory regions displayed similar amounts of activity (fig. S7V). However, in the abdomen, we observed a pronounced 83% reduction in activity of the dark allele regulatory region relative to that of the light allele (17 ± 3%) (Fig. 4, L and M, and fig. S7V). This decrease is very similar in magnitude to the reduction in *ebony* mRNA expression in the dark lines (Fig. 2). Thus, mutations in the dark line regulatory region affect gene expression with a high degree of spatial specificity and provide direct evidence that the modular architecture of cis regulatory regions minimizes the pleiotropic effects of functional mutations.

Multiple functional mutations underlie ebony enhancer evolution. To identify the position, number, kind, and size of effects of functionally relevant mutations within the *ebony* abdominal enhancer, we compared dark U76 and light U62 alleles because these represent the two extremes of *ebony* expression. Between the U76 and the U62 alleles, there are ~120 nucleotide differences scattered over the 2.4-kb abdominal enhancer [44 point mutations and 76 base pairs (bp) differing because of 10 insertions or deletions (indels)] that could potentially contribute to the observed difference in activity. To localize functional differences, we first created chimeric reporter constructs with groups of mutations and then narrowed these to individual changes that contribute to the activity of chimeric constructs. Our analysis below suggests that a minimum of five mutations differentiate the activities of dark and light lines, two of which are specific to the dark haplotype.

We focused on a 2.4-kb region that contained the 0.7-kb core abdominal element ("abd" in Fig. 4A) and recapitulated the difference in RNA expression between dark (U76) and light (U62) lines, such that the dark allele construct expressed 22% of the reporter activity of the light allele construct (fig. S8, B and C). We subdivided the 2.4-kb region into three subregions (X, Y, and Z, Fig. 5A) and systematically substituted individual fragments from the light allele into the dark allele construct. Of the three subregions tested, the Z fragment showed the strongest effect (fig. S8D), increasing reporter activity from 22% to 67% of the activity of the light allele. Moreover, in the reciprocal construct, swapping in the Z fragment was sufficient to decrease activity of the light allele from 100% to 46% activity (fig. S8E).

Several previously identified candidate mutations were only observed on the dark haplotype, the majority of which (five out of eight) map to the 2.4-kb regulatory region (fig. S8A, red bars labeled "Dark Specific Substitutions"). Replacement of all five substitutions in the dark allele construct with the nucleotides present in the light allele increased reporter activity to 70% of that of the light allele construct, demonstrating that they include functionally important mutations (fig. S8F). The Z fragment contains four of the five dark-specific mutations within the 2.4-kb element (fig. S8A), so we reverted the individual dark-specific substitutions of the dark allele construct. Dark-specific substitutions 2 and 3 showed no effect on the level of reporter expression (table S2), whereas substitution 4

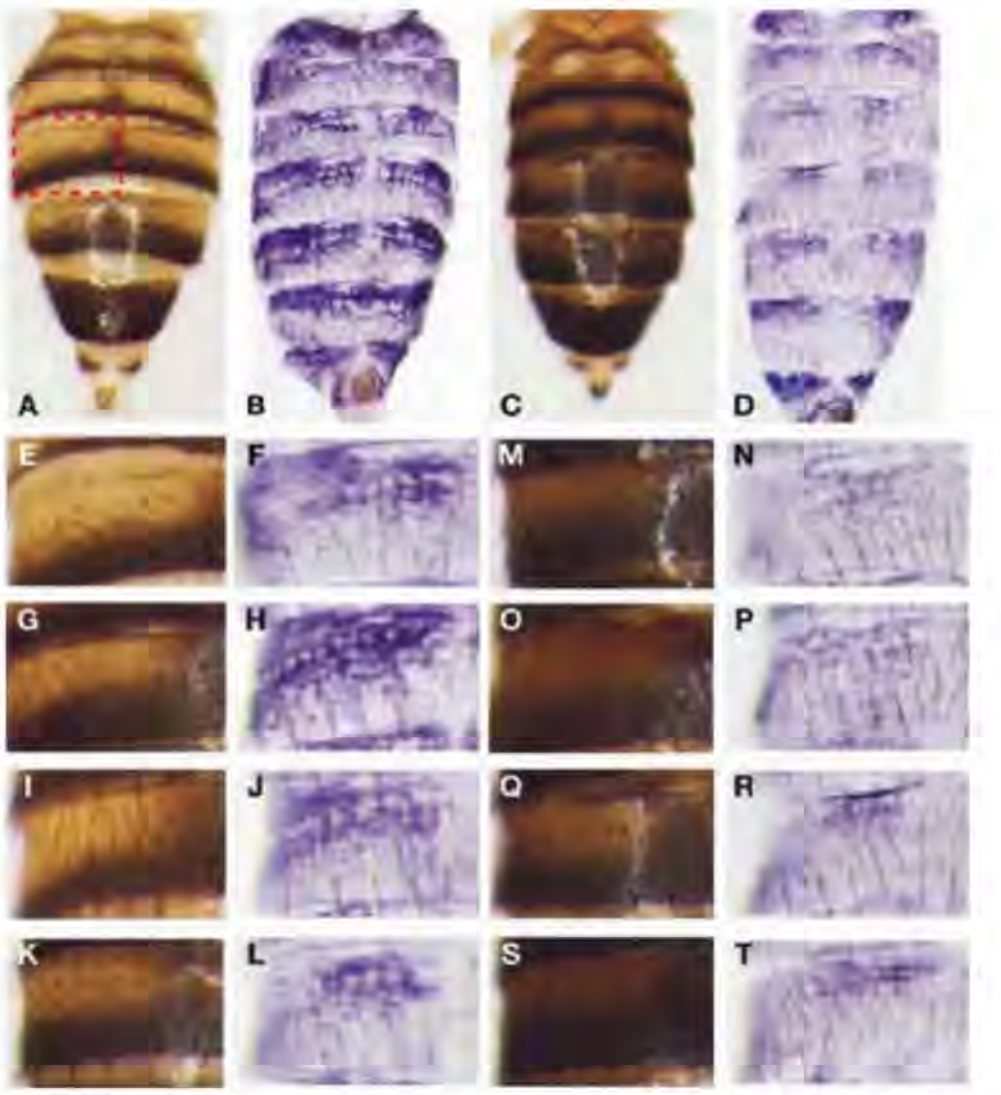

Fig. 2. *ebony* expression correlates with abdominal pigmentation within the Ugandan population. Abdominal pigmentation phenotypes of U53 (**A**) and U76 (**C**). The region outlined in (A) marks the A4 hemitergite imaged in (**E** to **T**). Accumulation of ebony transcript in the abdomen of U53 (**B**) and U76 (**D**) flies within 1 hour after eclosion was revealed by in situ hybridization. The developing U76 fly (C) shows greatly reduced amounts of *ebony* mRNA throughout the abdomen (D). [(E), (G), (I), (K), (M), (O), (Q), and (S)] Images of A4 hemitergite, as outlined in (A), from eight lines. [(F), (H), (J), (L), (N), (P), (R), and (T)] The corresponding amount of *ebony* mRNA expression within 1 hour post-eclosion revealed by in situ hybridization. Alleles are as follows: for (E) and (F), U53; (G) and (H), U62; (I) and (J), U64; (K) and (L), U65; (M) and (N), U75a; (O) and (P), U75b; (Q) and (R), U76; and (S) and (T), U78.

showed a small effect on expression, raising activity from 22% to 35% (fig. S8G). Substitution 5, however, caused a dramatic increase to 64% of the light allele activity (fig. S8H). Therefore, at least two novel substitutions in the Z fragment have contributed to the divergence of the dark and light haplotypes, with substitution 5 providing the largest effect.

To account for the remaining ~50% difference in activity, we turned to the X and Y fragments. No contribution of the X fragment (which contained dark-specific substitution 1) was observed when the light allele X fragment was swapped into the dark allele construct (fig. S8I). However, the chimeric construct bearing the Y fragment from the light line increased activity from 22% to 47% (fig. S8J), demonstrating that one or more functional mutations exist in the Y fragment. The Y fragment encompasses the core abdominal activity, the smallest span of DNA sufficient to drive strong reporter expression in the abdomen (figs. S6 and S8A). Comparison of the isolated Y fragment activities of the light and dark alleles also revealed much weaker activity of the dark allele Y fragment construct (25% relative to light) (fig. S9, B and C).

In order to pinpoint causative mutations within the Y fragment, we assayed a series of Y fragment GFP reporter constructs. Twenty-five point mutations and four indels (encompassing 42 bp) exist between the light U62 and dark U76 alleles Y fragment sequences. The major contribution to expression differences (81%) mapped to the 5′ half of the Y fragment (fig. S9, D and E), which allowed us to narrow the 67 candidate nucleotides down to the eight point mutations that differ in this region of the Y fragment (Fig. 5B). Of these eight candidates, three were eliminated because they were found in other strongly expressing Y fragments. We reverted each of the five remaining candidate substitutions individually from the dark allele to that present in the light allele. Mutations at positions 27 and 32 increased dark allele Y fragment activity from a 25% baseline to 54% and 50%, respectively, of the light allele Y fragment activity (fig. S9, F and G). The third substitution at position 137 had a more dramatic effect on the Y fragment activity, raising expression to 80% of light Y fragment expression (fig. S9H) (note that the sum of effects exceeds 100%, so individual effects are not strictly additive). These results suggest that at least three substitutions within the Y fragment contributed to the overall reduction of abdominal enhancer activity.

The five mutations that functionally differentiate the dark and the light haplotypes cause a decrease in the activity of the dark allele enhancer. The mutation with the greatest effect arose at a considerable distance (270 bp) from the core element. If this mutation is in an activator binding site, we would expect that this sequence would lie in the core element. Alternatively, the mutation may represent a repressor binding site. Indeed, when we deleted this site and the five adjacent nucleotides 5′ and 3′ to it, the enhancer drove a dramatic increase in reporter expression, from 22% to 106% of the light haplotype activities (fig. S8L). The greater effect of deleting these sites relative to reverting the nucleotide raised the possibility that these sites serve a function in the light allele. When we engineered the identical deletion into the light haplotype, reporter activity also increased (fig. S8M, 170% of light haplotype), indicating that this sequence is required to repress enhancer activity and that the substitution in the dark haplotype further repressed *ebony* expression.

Together, these data show that multiple mutations (at least five), with varying effects (accounting for 8% to 40% of the overall difference in activity) and representing different kinds of functional change (reduced activation strength, increased repression), underlie the evolution of the *ebony* abdominal enhancer.

Adaptive evolution via standing variation and new mutations. The observation that dark-specific substitutions accounted for a subset of the causative mutations raised the possibility that the path of *ebony* enhancer evolution involved both new mutations (the shared dark-specific substitutions) and standing variation (Fig. 5B). To assess the potential origins of the five substitutions, we examined the enhancer sequences of lines obtained from various regions in Africa (Fig. 5C).

The three causative substitutions located in the Y fragment occurred at high frequency in both light lines of the Ugandan population and in the light Kenyan population sample (Fig. 5B) and are also found in very distant African populations (Fig. 5C). Two of the substitutions were observed in all five populations sampled. The third Y fragment substitution was found in four of the five populations. These results demonstrate widespread standing genetic variation at the relevant sites in the Y fragment of the *ebony* abdominal enhancer.

The dark-specific substitutions were not observed in any other lines from Kenya or Uganda. Among 67 endemic fly lines from five African regions examined in our survey, the only other location where dark-specific mutations (numbers 4 and 5) occurred was in nearby Rwanda and was associated with the dark haplotype (Fig. 5C). The absence of these substitutions in isolation across the ancestral range of *D. melanogaster* indicates that they either arose de novo or were rare variants present in the population when the dark haplotype was selected.

The existence of both common polymorphisms and rare substitutions contributing functional changes to *ebony* expression raised the

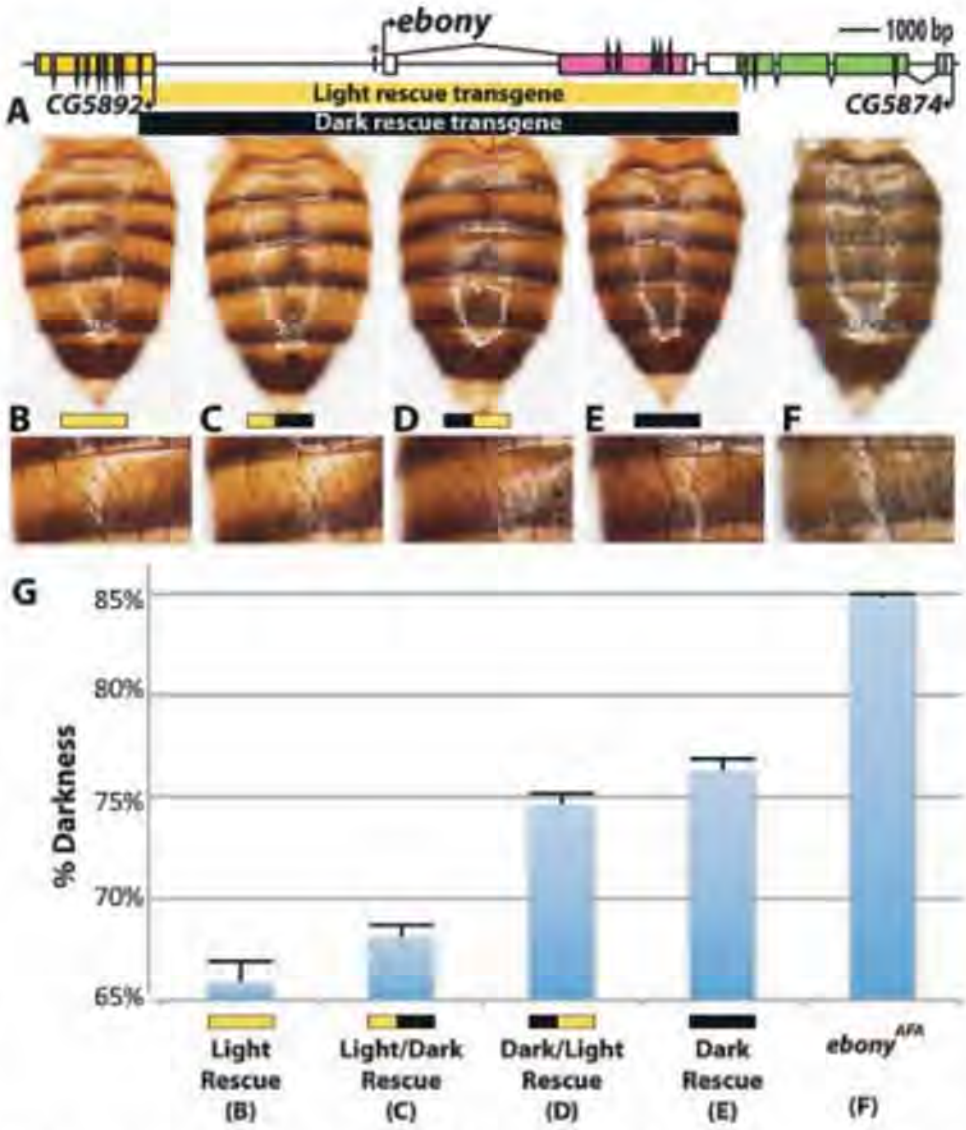

Fig. 3. Noncoding variation at *ebony* causes abdominal melanism. By using transgenic complementation, we localized abdominal pigmentation differences between light and dark *ebony* alleles to the 5′ noncoding region. (**A**) Schematic of the *ebony* gene, indicating the span of rescue transgenes tested. The asterisk denotes the location at which light/dark chimeric transgenes were fused. Rescue transgenes were transformed into *D. melanogaster* and crossed into an *ebony* null mutant background [(**F**), $ebony^{AFA}$]. (**B**) Rescue of the *ebony* mutant abdominal phenotype by one copy of a U62 (Light) *ebony* transgene. (**C**) Animal bearing one copy of a chimeric transgene consisting of the 5′ regulatory region from the light line and the transcription unit of the *ebony* gene of a dark line displays a light abdominal phenotype that is similar to the light line. (**D**) A fly bearing the dark line's 5′ regulatory region fused to the transcription unit of the light allele shows a dark phenotype that is similar to the dark line rescue transgene phenotype. (**E**) A rescue transgene derived from the dark line U76 complements the *ebony* mutation to a much lesser degree than the light line transgene. (**G**) Quantification of the amount of abdominal phenotypic rescue by transgenes. Letters below each column label correspond to the images above. Bars indicate standard error of the mean.

potential scenario that the relevant haplotype of standing variation in the Y fragment was assembled before dark-specific substitutions appeared and adaptive selection resulted in their high frequency. To test this scenario and to place these functional changes on a relative time scale, we took note of a Ugandan line (U65) that exhibited intermediate pigmentation (Fig. 1), *ebony* expression (Fig. 2, K and L), and abdominal enhancer activity (fig. S8K). Of all the nonmelanic lines examined, the Y fragment of U65 was most similar to the dark haplotype Y fragment, harboring all three functionally relevant Y fragment mutations (Fig. 5B) and sharing a ~1-kb region of sequence similarity with the dark line haplotype.

Within the 0.9-kb tract of polymorphisms shared between U65 and the dark strain haplotype, four mutations have arisen that differentiate the two, allowing us to estimate that they shared a common ancestor about 395,000 generations ago (SOM text). In contrast, the dark haplotype has accumulated just three substitutions across 14 kb among four lines, suggesting that these four alleles last shared a common ancestor only about 9000 generations ago. The 95% confidence intervals for these estimates do not overlap, which allows us to infer that the Y fragment haplotype existed long before the dark-specific substitutions arose (fig. S10). Hence, we have resolved two steps in the evolution of this adaptation: the assembly of functional standing variation followed by the recent addition of beneficial dark-specific substitutions that resulted in the full decrease of *ebony* expression, caused pronounced abdominal melanism, and which were swept to high frequency (fig. S11).

The genetic path of enhancer evolution. We have shown that the adaptive evolution of melanism in a Ugandan population of *D. melanogaster* occurred through multiple, stepwise substitutions in one enhancer of the *ebony* locus. We suggest that this genetic path of enhancer evolution with multiple substitutions of varying effect sizes, which originate from both standing variation and new mutations and combine to create an allele of large effect, may be a general feature of enhancer evolution in populations. This view is consistent with studies that have demonstrated that substitutions at multiple sites within enhancers are responsible for evolutionary changes in gene expression (*6*, *7*, *19*–*22*).

The pattern of multiple substitutions in enhancers also makes sense in light of their functional organization. Enhancers contain numerous transcription factor binding sites that are broadly distributed across a few hundred base pairs or more, all of which contribute to overall transcriptional output. Variation in enhancer output can and does arise from modifications at any of a large number of sites, and functional standing variation in enhancers is abundant in populations (*23*, *24*).

Enhancers and proteins are very distinct macromolecular entities, and it is useful to consider

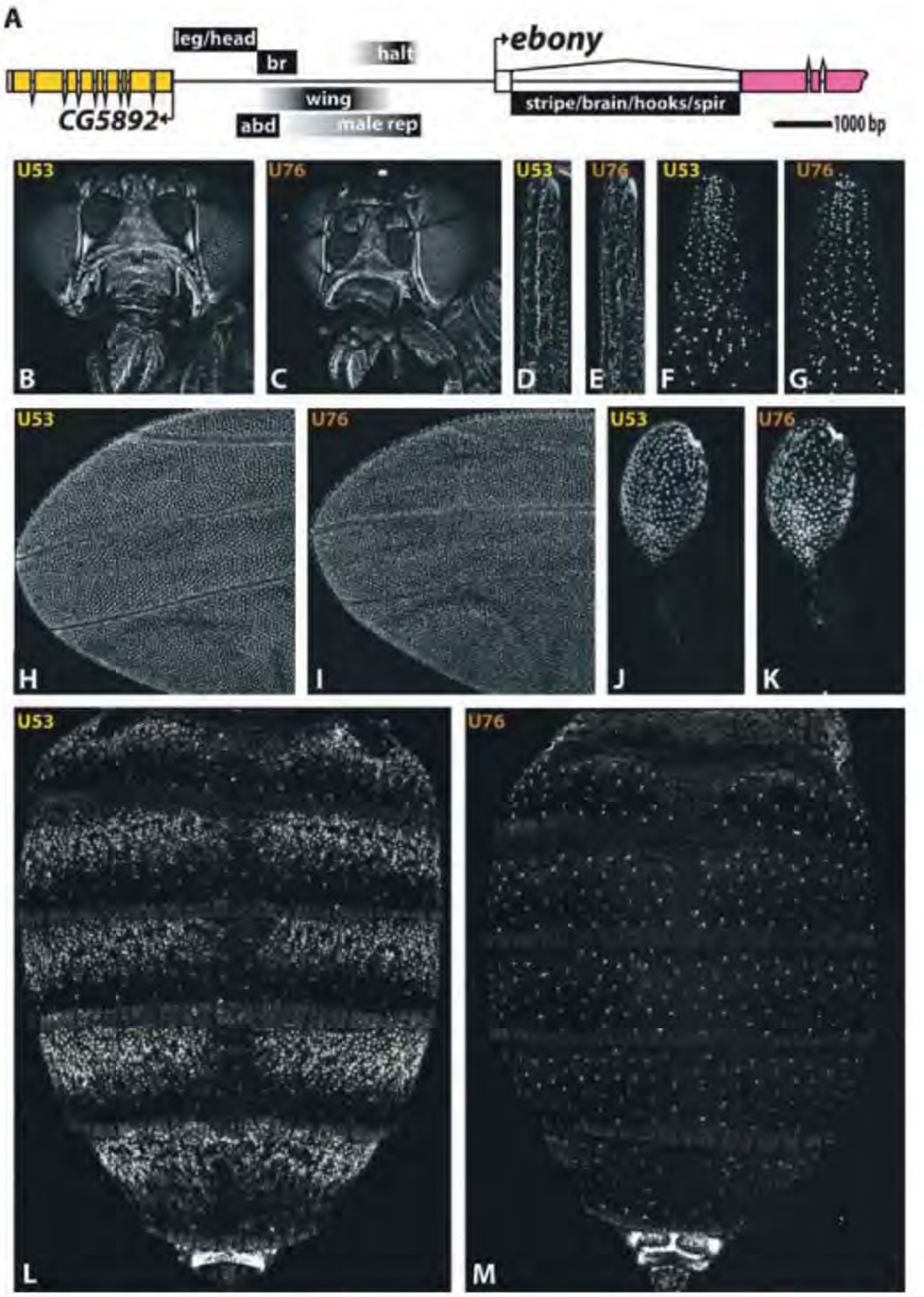

Fig. 4. The divergence in *ebony* activity is confined to a modular enhancer. Localization of *ebony* regulatory sequences in a GFP reporter assay; the difference in activity between light and dark alleles is restricted to the abdomen. (**A**) Map of ebony locus displaying the location of enhancers mapped through reporter assays. Black bars denote regions required for activity, whereas gray areas delineate the area in which enhancer boundaries lie. br indicates bristles; male rep, male repression; halt, haltere; stripe, abdominal tergite stripe repression; brain, third instar larval brain; hooks, larval mouth hooks; and spir, larval spiracles. (**B** to **M**) Reporter activity driven by the complete regulatory region of the *ebony* locus from a light [U53 in (B), (D), (F), (H), (J), and (L)] or dark [U76 in (C), (E), (G), (I), (K), and (M)] chromosome extraction line. Shown in (B) and (C) is the head; (D) and (E), femur of T2 legs; (F) and (G), third instar brain; (H) and (I), wing; (J) and (K), haltere; (L) and (M), adult abdomen. Staging and fluorescence quantification are presented in SOM text.

the potentially different constraints operating on enhancers and proteins that might affect their evolutionary trajectories. At least five constraints limit variation within proteins and restrict the path of protein evolution. The first constraint is pleiotropy. Coding mutations in pleiotropic genes will generally affect all functions, which will most likely be deleterious. The second constraint is the triplet genetic code that cannot accommodate most indels. Third, proteins must fold properly, and most random amino acid replacements are destabilizing and deleterious (*25*, *26*). Fourth,

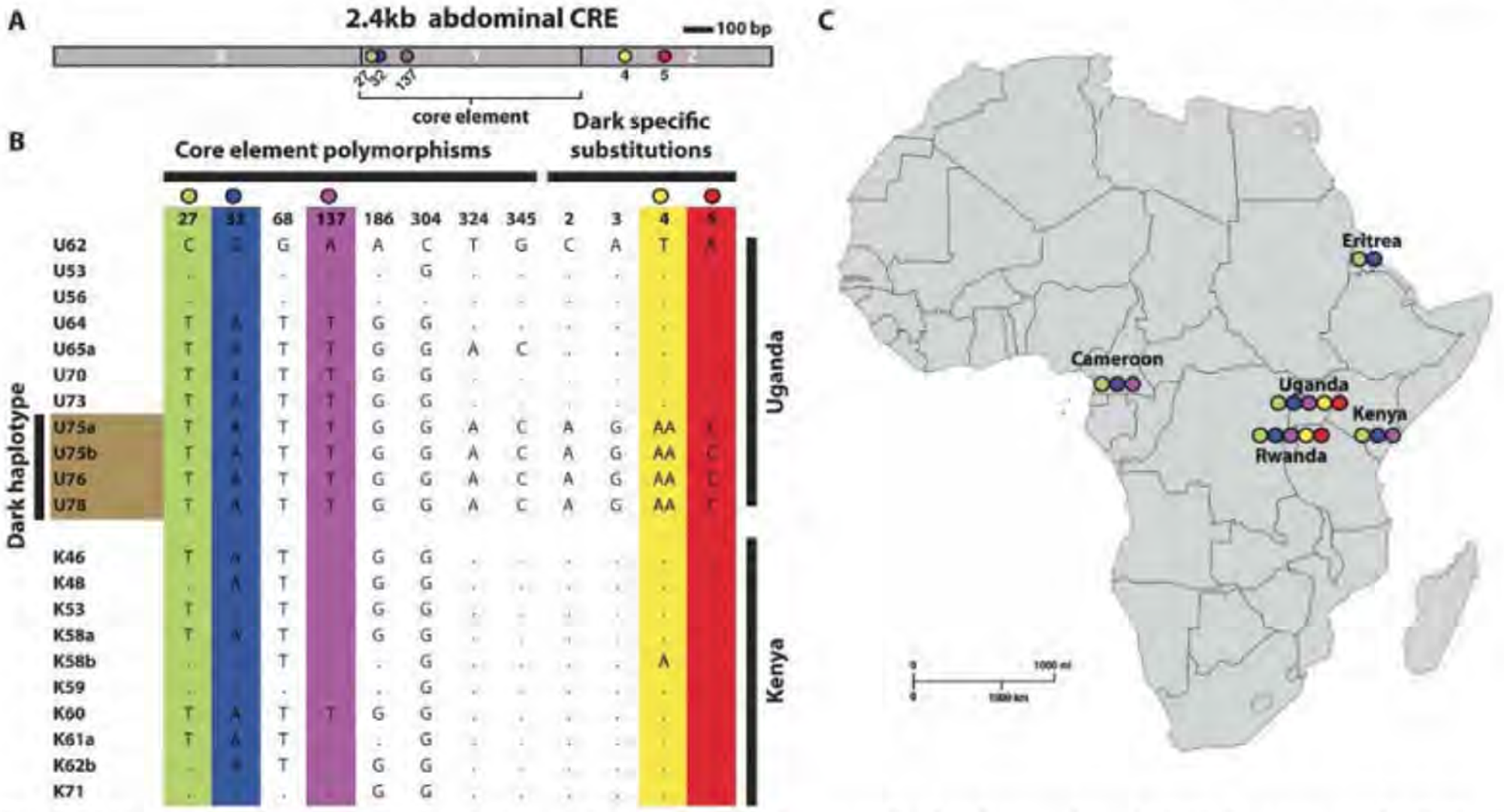

Fig. 5. Multiple mutations in the *ebony* abdominal cis regulatory element contribute to enhancer activity differences. Five mutations decrease ebony expression in the dark allele and show a varied distribution across Africa. (**A**) Schematic of *ebony* abdominal enhancer, showing the positions of the X, Y, and Z fragments and the relative position of identified causative mutations. (**B**) Candidate mutations in the core element and the dark-specific substitutions that were tested by reporter assay. Colored shading of residues highlights mutations with functional contribution to enhancer divergence. Numbers for core element substitutions correspond to the base pair position of each nucleotide within the minimal abdominal element. Numbers below dark-specific substitutions coincide with their order in the region of the abdominal element (see fig. S9 for a schematic representation). (**C**) Map of African continent displaying distribution of causative mutations identified in the study. The color coding for mutations corresponds to the shading and colored circles above each relevant mutation in (A).

because of demands on protein structure, the order in which specific amino acid replacements may occur is typically constrained (*13*, *14*), thus reducing the number of genetic paths adaptation may take. And lastly, many proteins often have a single active site or one or a few binding domains, such that changes at only a very limited number of positions may directly alter properties of these sites.

In contrast, more relaxed constraints appear to operate on evolving regulatory elements. The evolution of individual, modular enhancers circumvents the pleiotropic effects of coding mutations, and our results illustrate precisely why this is the case. Obviously, there is no triplet code, so a greater range of mutational events can be accommodated. Furthermore, enhancers are not constrained by three-dimensional structure; consequently, the order in which substitutions may occur would appear to be much less constrained. Indeed, we found many combinations of functionally relevant polymorphisms in our survey of *ebony* haplotypes. In addition, chimeric enhancers that placed more recent mutations in an ancestral context exhibited intermediate levels of function, as would be expected if multiple alternate genetic paths are viable. And lastly, because enhancers generally contain numerous binding sites for transcription factors distributed throughout their sequence, there may be more potential sites where substitutions may modify function. Here, we identified substitutions that both decreased activation and increased repression. Thus, during their respective paths of adaptation, enhancers may present a larger mutational target for functional modification and may have a greater number of possible genetic paths open to them relative to typical protein-coding sequences.

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Materials and Methods
SOM Text
Figs. S1 to S11
Tables S1 to S4

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Crystal Structure of the Eukaryotic Strong Inward-Rectifier K^+ Channel Kir2.2 at 3.1 Å Resolution

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Inward-rectifier potassium (K^+) channels conduct K^+ ions most efficiently in one direction, into the cell. Kir2 channels control the resting membrane voltage in many electrically excitable cells, and heritable mutations cause periodic paralysis and cardiac arrhythmia. We present the crystal structure of Kir2.2 from chicken, which, excluding the unstructured amino and carboxyl termini, is 90% identical to human Kir2.2. Crystals containing rubidium (Rb^+), strontium (Sr^{2+}), and europium (Eu^{3+}) reveal binding sites along the ion conduction pathway that are both conductive and inhibitory. The sites correlate with extensive electrophysiological data and provide a structural basis for understanding rectification. The channel's extracellular surface, with large structured turrets and an unusual selectivity filter entryway, might explain the relative insensitivity of eukaryotic inward rectifiers to toxins. These same surface features also suggest a possible approach to the development of inhibitory agents specific to each member of the inward-rectifier K^+ channel family.

In 1949 Bernard Katz introduced the term "anomalous rectification" to distinguish the K^+ currents he observed in frog skeletal muscle from the "delayed rectification" K^+ currents of the squid axon action potential (*1*, *2*). Today we know that "delayed rectifiers" are a subset of the large family of voltage-dependent K^+ (Kv) channels, whereas "anomalous rectifiers" are members of a different family of channels more commonly known as inward-rectifier K^+ (Kir) channels (*3*). The name "inward rectifier" refers to a fundamental ion-conduction property exhibited to a greater or lesser degree by all members of the family: Given an equal but opposite electrochemical driving force, K^+ conductance into the cell far exceeds conductance out of the cell. Thus, Kir channels are analogous to one-way conductors, or diodes, in solid-state electronic devices.

Electrophysiological experiments have shown that inward rectification is a consequence of voltage-dependent pore blockage by intracellular multivalent cations, especially Mg^{2+} and polyamines (*4*–*8*). At internal negative (hyperpolarizing) membrane voltages, the blocking ions are cleared from the pore so that K^+ conducts, whereas at internal positive (depolarizing) membrane voltages the blocking ions are driven into the pore from the cytoplasm so that K^+ conduction is blocked. As a result, Kir channels are conductive when an excitable cell is at rest and nonconductive during excitation. This property is thought to foster energy efficiency because it enables Kir channels to regulate the resting membrane potential, but not dissipate the K^+ gradient during an action potential (*3*).

A central mechanistic question is, why are Kir channels blocked by intracellular multivalent cations? Mutational studies have identified several amino acids that confer sensitivity to blocking ions (*9*–*19*), but a structural description of these sites has remained elusive. Structures of prokaryotic Kir channels, because of their low sequence similarity to eukaryotic Kir channels, do not contain the specific amino acids that are known to underlie blockage and rectification (*20*, *21*).

Another long-standing puzzle in eukaryotic Kir channel studies is their relative insensitivity to natural toxins that typically inhibit other K^+ channels (*22*–*24*). Snake, spider, and scorpion venoms, for example, contain numerous toxins against various Kv channels and Ca^{2+}-activated K^+ channels (*25*–*27*). By contrast, Kir channel toxins are rare, and no specific toxins against Kir2 channels have been discovered.

Eukaryotic Kir channels as a molecular family. The eukaryotic Kir channels contain several amino acid sequence motifs and conserved amino acids that are essential to their functional properties (Fig. 1). For example, in most other K^+ channels the selectivity filter comprises the "canonical" filter sequence TXGYGDX, where X represents an aliphatic amino acid (Fig. 1). The corresponding sequence in eukaryotic Kir channels is TXGYGFR, with F sometimes replaced by another amino acid. In light of the structural importance of DX in the canonical sequence, the amino acids FR signify a marked variation on the filter sequence. Eukaryotic Kir channels also contain an absolutely conserved pair of cysteine residues flanking the pore region, which is the reentrant peptide segment that forms the pore helix and selectivity filter of K^+ channels. Between the outer helix (the first transmembrane segment) and pore region the "turret," though varied among inward rectifiers, contains the sequence HGDL that could be considered a signature of eukaryotic Kir channels. Finally, through extensive studies combining electrophysiology and mutagenesis, several acidic amino acids (D and E) are known to be critical to inward rectification (*9*–*19*), and motifs containing basic amino acids (e.g., PKKR) are critical to phosphatidylinositol 4,5-bisphosphate (PIP_2) activation of Kir channels (*28*–*35*). These positions are highlighted on the sequences in Fig. 1.

The Kir2.2 channel from chicken is 90% identical to the human ortholog (excluding the N and C termini) and contains all of the sequence characteristics of a strong inward rectifier (*36*). Figure S1 shows that the chicken Kir2.2 channel expressed in *Xenopus* oocytes indeed functions as a strong rectifier. In oocyte two-electrode voltage-clamp recordings with 98 mM KCl in the bath solution, inward currents are much larger than outward currents (fig. S1B). In on-cell and excised gigaseal patch recordings, channel activity is observed at hyperpolarizing (negative internal) membrane voltages but not at depolarizing (positive internal) voltages (fig. S1C). The single-channel conductance measured near −80 mV is ~40 pS, which is very similar to the values reported for the guinea pig and mouse Kir2.2 channels (*37*, *38*) (fig. S1D, inset). The sharp transition between channel conductance and nonconductance as a function of membrane voltage is characteristic of a strong rectifier (*36*). Upon patch excision from the oocyte surface, some outward current is observed at voltages slightly positive to the reversal potential because the concentration of intracellular blockers is decreased (fig. S1C, blue trace). However, the current still decreases with further depolarization (negative conductance) as channels become blocked in a voltage-dependent manner; this behavior reflects the inherent difficulty in washing away trace yet still active concentrations of polyamine molecules due to their very high affinity for the pore in strong rectifiers (*39*, *40*). Several minutes after patch excision, the currents decrease (fig. S1C, red trace). This "run-down" reflects altered channel regulation mediated by kinases, phosphatases, and lipid signaling (*34*, *36*, *41*, *42*).

To obtain diffracting crystals, we removed the intrinsically disordered N- and C-terminal regions. The electrophysiological recordings shown in fig. S1 were made using a similar construct with N- and C-terminal truncations, confirming that the crystal structure corresponds to a functional channel unit with strong rectifying properties. The Kir2.2 model, consisting of the cytoplasmic domain and transmembrane channel, was refined at 3.1 Å to a free *R*-factor of 0.27. A ribbon diagram in stereo shows the transmembrane pore (above) and the cytoplasmic pore (below) (Fig. 2A). Lateral openings between the transmembrane and cytoplasmic pores, at the level of the lipid membrane headgroup layer, contain many arginine and lysine residues. The high density of positive charges makes it unlikely that K^+ ions would pass through these openings (fig. S2). The structure is therefore consistent with mutagenesis studies, which support the conclusion that

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the ion pathway extends across the full length of the transmembrane and cytoplasmic pores (*9*–*19*). The overall architecture is similar to that of prokaryotic Kir channels but with a notable difference: The Kir2.2 channel contains prominent, highly structured turrets on the extracellular face of the channel. These surround, as if to protect, the pore entryway.

The selectivity filter. At a detailed structural level, Kir2.2 is quite different from prokaryotic Kir channels owing to minimal (<20%) sequence conservation. The cysteine pair that is absolutely conserved among eukaryotic Kir channels creates a circularized pore region through covalent linkage of the segment preceding the pore helix (C123) to the segment following the selectivity filter (C155) (Fig. 2B). The existence of a disulfide bond was correctly predicted on the basis of mutagenesis studies: Mutation of the corresponding cysteines in Kir2.1 led to the absence of currents even though expressed protein was detectable by Western blot analysis (*43*, *44*). Application of 10 mM dithiothreitol (DTT) or reduced glutathione to the outside of cells expressing the wild-type channels did not affect currents. From these two observations it was concluded that a disulfide bridge must be essential for proper folding, but apparently not for function (*43*, *44*). The structure provides an alternative interpretation. The disulfide bridge is buried beneath the protein surface at the level of the membrane interface. Furthermore, the Kir2.2 channel was purified and crystallized in the presence of 20 mM DTT and 3 mM TCEP [(tris(2-carboxyethyl)phosphine)], and yet the disulfide bridge remained intact. It is therefore possible that the disulfide bridge remains intact upon exposure to moderate concentrations of DTT and that the bridge may be important for channel function.

The pore region is further stapled together by an ionized hydrogen bond between R149 in the filter sequence TXGYGFR and E139 (Fig. 2, B and C). The Glu O-ε to Arg N-η distance is 2.4 Å, compatible with an energetically strong interaction. Mutations altering this interaction are known to alter channel function (*45*, *46*). On the basis of studies with concatenated subunits, the salt bridge was thought to be intersubunit, but the crystal structure shows that this interaction ties together two segments of the pore region within a single subunit (*46*).

Despite the presence of substantially different protein contacts surrounding the selectivity filter, the main-chain structure of the filter in Kir2.2 is the same as in other K^+ channels (*47*). For example, the main-chain root mean square deviation between Kv1.2 and Kir2.2 is 0.4 Å, which is within the margin of certainty to discriminate atomic positions with 3.1 Å diffraction data (Fig. 2, D and E) (*20*, *48*, *49*). One structural difference near the filter could possibly account for important pharmacological differences between Kir and other K^+ channels. In the canonical filter sequence, the Asp (D) residue in the filter sequence is buried, creating a flat surface surrounding the filter opening. By contrast, in Kir channels, the Phe (F) residue at the corresponding position projects directly into

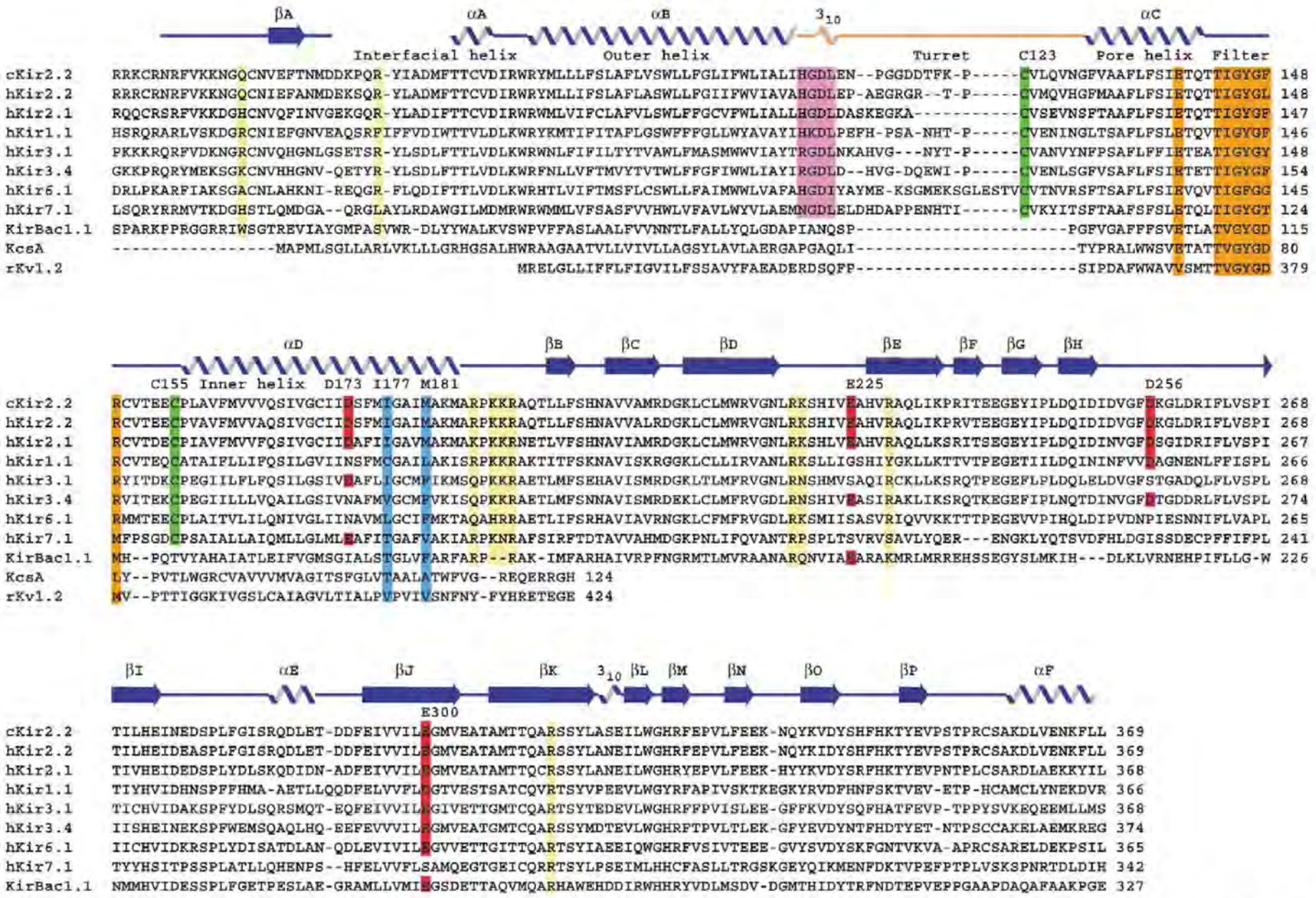


Fig. 1. Key residues in eukaryotic Kir channels. Sequence alignment of chicken Kir2.2 (GI: 118097849), human Kir2.2 (GI: 23110982), human Kir2.1 (GI: 8132301), human Kir1.1 (GI: 1352479), human Kir3.1 (GI: 1352482), human Kir3.4 (GI: 1352484), human Kir6.1 (GI: 2493600), human Kir7.1 (GI: 3150184), KirBac1.1 (GI: 33357898), KcsA (GI: 39654804), and rat Kv1.2 (GI: 73536156). For all the Kir sequences, only the core region corresponding to the expressed protein and atomic structure of Kir2.2 is included in the alignment. For Kv1.2, only the transmembrane pore region is shown. Secondary-structure elements are indicated above the sequences, and the turret is colored orange. Residues discussed in the text are highlighted in red (acidic residues), green (two disulfide-bonded cysteines), cyan (the inner helix bundle activation gate), purple (conserved residues among the turrets of eukaryotic Kir channels), orange (the selectivity filter and E139), and yellow (critical residues for channel-PIP_2 interactions). Abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

aqueous solution, creating four protrusions on the perimeter where the filter opens to the extracellular solution.

The cavity and gates. The pore lining on the intracellular side of the selectivity filter is mainly hydrophobic in nearly all K^+ channels. Eukaryotic Kir channels are an exception in which the central region of the pore—known as the central cavity—contains four polar amino acids (one from each subunit) projecting toward the ion pathway (Fig. 3, A and B). In Kir2.2 and other strong rectifiers, these polar amino acids are Asp (D173), whereas in weak rectifiers such as Kir1.1 and Kir6.1 they are Asn (Fig. 1). On the basis of electrophysiological studies, Asp residues in the central cavity of strong rectifiers are hypothesized to influence the affinity of Mg^{2+} and polyamines by an electrostatic mechanism (*12*, *18*).

Beneath the central cavity, residues I177 and M181 on the inner helices form two hydrophobic seals that close off the pore leading to the cytoplasm (Fig. 3C). Kir2.2 is therefore physically shut at the "activation gate" (*50*). Amino acids corresponding to positions 177 and 181 are also large and hydrophobic in most other eukaryotic Kir channels, but not in many other K^+ channels (Fig. 1). For example, in KcsA, Kv channels, and prokaryotic Kir channels, the position corresponding to 177 usually contains a small and sometimes polar amino acid, typically Val or Thr. In KcsA, both seal positions contain small amino acids (Fig. 3D). Because of the large hydrophobic residues at positions 177 and 181, the inner helices of Kir2.2 do not come as close together in the closed conformation as in KcsA (Fig. 3, C and D).

Figure 3E shows the cytoplasmic domain tetramer from the Kir2.2 channel superimposed onto the domain from Kir2.1, which was solved by crystallography in the absence of a transmembrane channel (*11*). Over most of the domain, these structures are nearly identical. This observation supports the expectation (based on 80% sequence identity) that Kir2.2 should represent an excellent model for the complete Kir2.1 channel. In addition to the activation gate formed by the transmembrane inner helices, Kir channels have been proposed to have a second gate (G loop) at the apex of the cytoplasmic domain tetramer (*11*, *51*). The G loop is physically open in Kir2.2 and closed in the Kir2.1 domain (Fig. 3, F and G). The differences in conformation are due to local movements of the G loop rather than to rigid body motions of the cytoplasmic domains. Local G loop movements contrast observations on the cytoplasmic domain of Kir3.1, in which the G loop opening appears associated with rigid body movements of domains in the tetramer (*20*).

Ion binding sites for conduction and inward rectification. Figure 4, A to F, shows the locations of ions in difference Fourier maps from crystals containing Rb^+, Sr^{2+}, and Eu^{3+}. Rb^+ is a K^+ analog that conducts current.

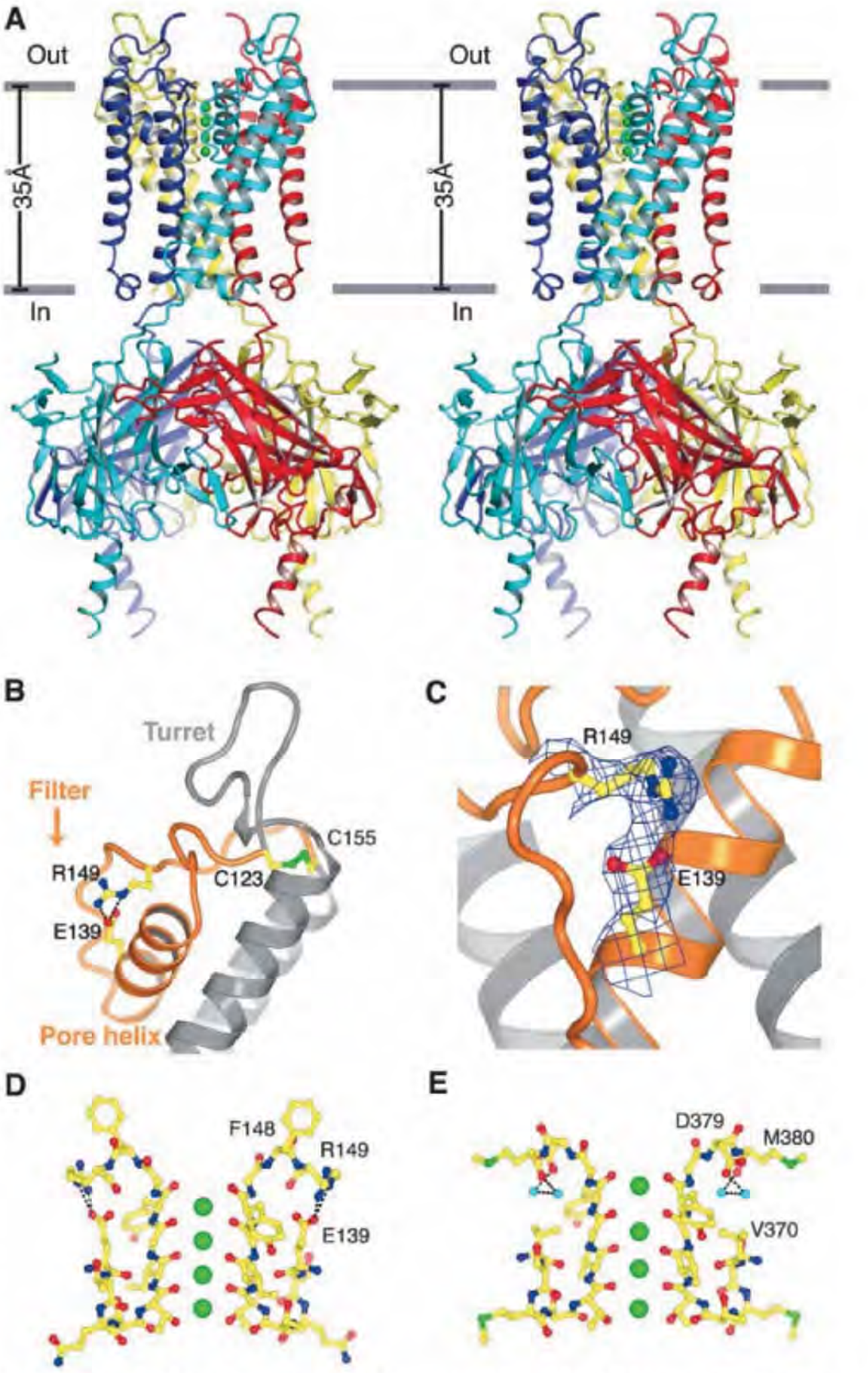
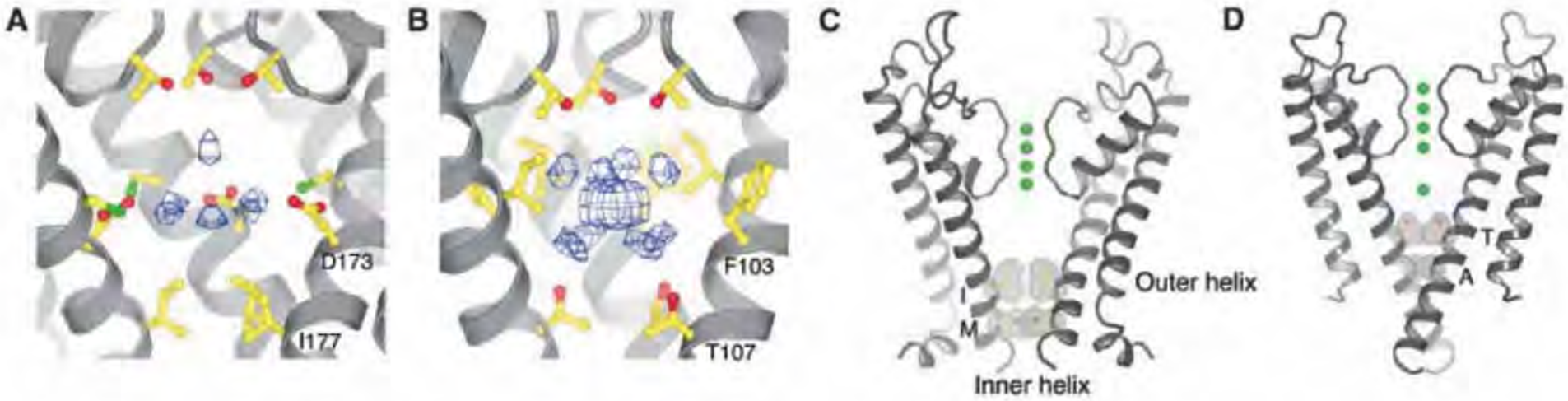


Fig. 2. Structure of Kir2.2. (**A**) Stereoview of a ribbon representation of the Kir2.2 tetramer from the side with the extracellular solution above. Four subunits of the channel are uniquely colored. Approximate boundaries of the lipid bilayer are shown as gray bars. (**B**) A close-up view of the pore region of a single subunit (in ribbon representation) with the turret, pore helix and selectivity filter labeled. Side chains of residues E139, R149 and a pair of disulfide-bonded cysteines (C123 and C155) are shown as sticks and colored according to atom type: carbon, yellow; nitrogen, blue; oxygen, red; and sulfur, green. Ionized hydrogen bonds are indicated by dashed black lines. The region flanked by the two disulfide-bonded cysteines is colored orange. (**C**) Electron density (blue wire mesh, $2F_o - F_c$, calculated from 50 to 3.1 Å using phases from the final model and contoured at 1.0 σ) is shown for the side chains of E139 and R149 [sticks, colored the same scheme as in (B)] forming a salt bridge. (**D** and **E**) K^+ selectivity filter of the Kir2.2 channel (D) compared with that of the Kv1.2-Kv2.1 paddle chimera channel [(E), PDB ID 2R9R]. For clarity, only two of the four subunits [sticks, colored with the same scheme as in (B)] are shown. K^+ (green spheres), water molecules (cyan spheres), and hydrogen bonds between R149 and E139 (Kir, dashed black lines), or between D379, M380 and waters (Kv, dashed black lines), are shown.

Density for this ion is observed at multiple sites in the selectivity filter and at three positions within the pore on the intracellular side of the selectivity filter, but is absent in the central cavity (Fig. 4A). The three occupied intracellular positions are as follows: immediately internal to the activation gate in the transmembrane pore, in the cytoplasmic pore internal to the G loop, and at the entryway to the cytoplasmic pore. We refer to the two sites in the cytoplasmic pore as the upper and lower rings of charges, respectively (fig. S3). The presence of multiple sites along the pore occupied by conducting ions is a prerequisite for strong voltage-dependent block by intracellular cations that cannot pass through the selectivity filter (*12*, *52*–*57*).

Crystals of Kir2.2 were grown in the presence of 650 mM Rb^+ and yet electron density for Rb^+ is not observed in the cavity (Fig. 4A). This finding is noteworthy because under similar conditions, a strong monovalent cation peak is observed in the cavity of KcsA (*47*, *58*). Native crystals of Kir2.2, grown in the presence of 150 mM K^+ and 500 mM Na^+, show a weak electron density peak at the cavity center with additional peaks on the perimeter, apparently bridging toward the D173 side chain (Fig. 3A). We cannot discern whether these peaks represent a disordered ion, multiple ions, or a low-occupancy K^+ (or Na^+) in the center, perhaps surrounded by water molecules hydrogen bonded to the Asp carboxylate. We can conclude, however, that the central cavity in Kir2.2, at least in the closed conformation, has cation-attractive properties that are different from those of KcsA.

The divalent cation Sr^{2+} should behave as an electron-dense mimic of Mg^{2+}, a biologically important metal-ion inhibitor of eukaryotic Kir channels (*7*, *8*). In $F_o - F_c$ Fourier maps from crystals with 10 mM Sr^{2+}, 500 mM Na^+, and 150 mM K^+, density peaks due to Sr^{2+} are observed at three sites inside the pore intracellular to the selectivity filter: in the cavity, at the upper ring, and at the lower ring of charges (fig. S3 and Fig. 4B). The magnitude of the Sr^{2+} peak is small in the cavity (3.4 σ) compared to the peaks at the upper (9.6 σ) and lower (7.2 σ) rings of charges. Separate experiments with crystals containing 200 mM Sr^{2+} support the notion that the weak cavity peak is indeed due to Sr^{2+}, which is present apparently at relatively low occupancy. Detailed views of these sites are shown (Fig. 4, D to F). They each consist of planar rings of acidic amino acids arranged on the pore's perimeter. All three sites exhibit a preference for Sr^{2+}: 10 mM Sr^{2+} outcompetes 150 mM K^+. This selectivity is likely to be electrostatic in origin. The sites are too wide (10.5, 8.9, and 9.3 Å diameter for the cavity, upper, and lower ring of charges) to mediate direct coordination of an ion at the center. Presumably ions at the center of these sites interact through bridging water molecules. Because each site has the potential to contain multiple negatively charged carboxyl groups, the resulting strong electric field is expected to



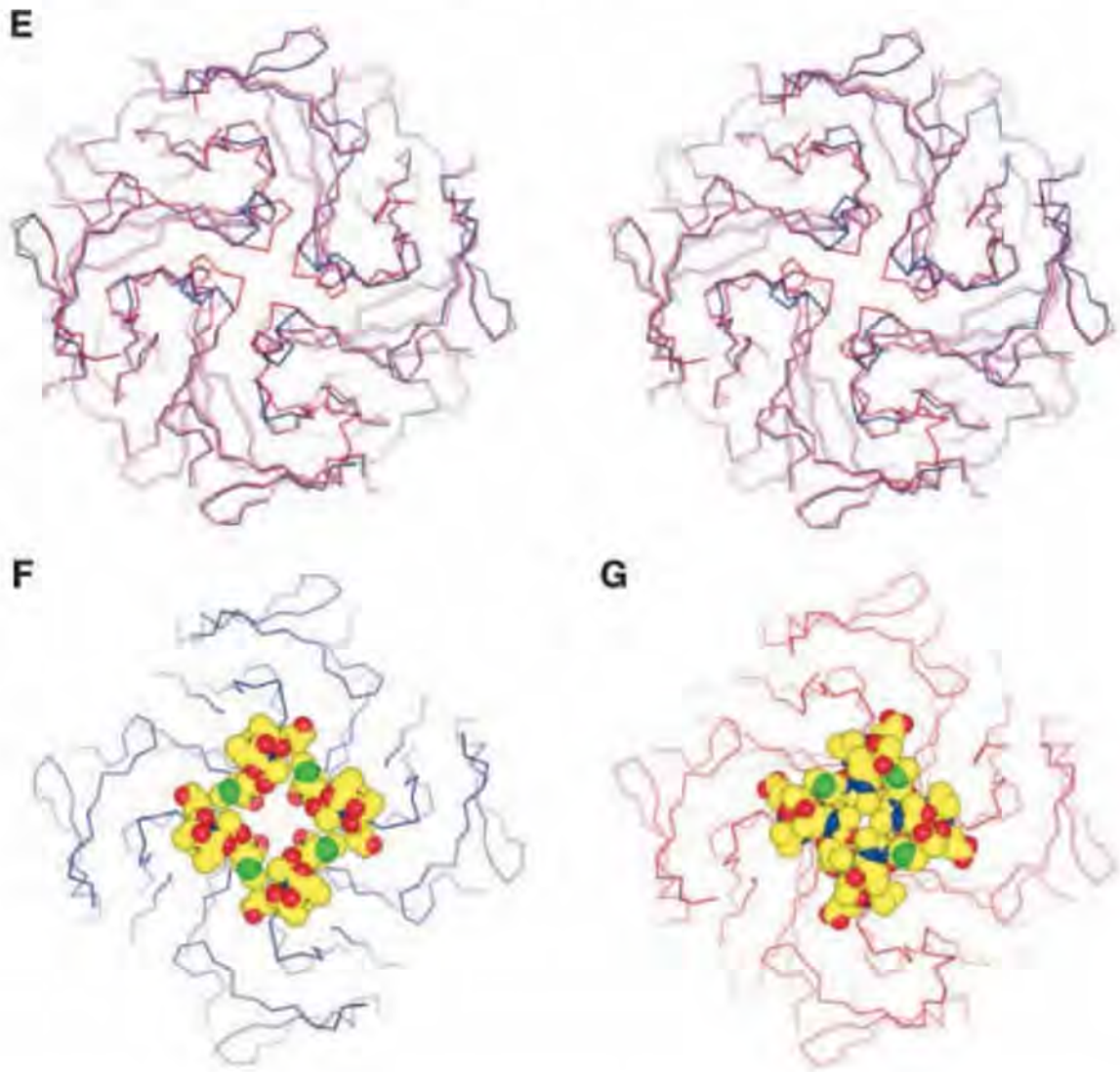


Fig. 3. The cavity and gates. (**A** and **B**) Electron density in the cavity of the Kir2.2 channel [(A), $F_o - F_c$ omit map, calculated from 50 to 3.1Å using phases from the final model and contoured at 2.0 σ] and of the KcsA channel [(B), PDB ID 1K4C, $F_o - F_c$ omit map, calculated from 50 to 3.1Å using phases from the final model and contoured at 2.8 σ]. The channels are shown as ribbon representations with the subunit closest to the viewer removed. Only the side chains facing the cavity are shown (sticks). (**C** and **D**) Comparison of the transmembrane inner helix bundle activation gate of Kir2.2 (C) with the KcsA structure [(D), PDB ID 1K4C]. For clarity, only two of the four subunits (gray ribbon) are shown. Side chains of the residues in the bundle crossing are shown as sticks [colored with the same scheme as in (B)] and van der Waals surfaces (gray dots). K^+ ions are shown as green spheres. Inner and outer helices are indicated. (**E**) Superposition of the chicken Kir2.2 cytoplasmic domain (blue α-carbon trace) and the mouse Kir2.1 cytoplasmic domain (red α-carbon trace, PDB ID 1U4F) in stereo viewed from the extracellular side. (**F** and **G**) Comparison of the apex (G loop) of the cytoplasmic pores of Kir2.2 (F) and mouse Kir2.1 (G), with the same view as (E). The cytoplasmic domains are shown as α-carbon traces, with residues 303 to 309 (Kir2.2) and 302 to 308 (Kir2.1) shown as CPK models (carbon, yellow; nitrogen, blue; oxygen, red; and sulfur, green).

create a good match for a multivalent cation. Crystals containing the lanthanide Eu^{3+}, which we assume to be trivalent (*59*), provide support for this hypothesis. An anomalous difference Fourier map shows that Eu^{3+} binds at only one site, the upper ring of charges (Fig. 4C). This site appears to be more electronegative than the others because it contains two concentric rings of acidic amino acids, E225 and E300.

Mutagenesis studies have identified several amino acids that, when mutated, affect the affinity of Mg^{2+} and polyamines in strong rectifiers. D173 in the cavity, E225 and E300 forming the upper ring of charges, and D256 forming the lower ring of charges are among those known to be important (*9*–*19*). The weak Sr^{2+} peak in the cavity might seem incompatible with the large influence that mutations of the cavity Asp (D173) have on Mg^{2+} affinity. However, the channel in the crystal is not in an applied electric field: In an electric field imposed by a depolarized (positive inside) membrane, we expect that the distribution of blocker occupancies among the multiple sites will change. Specifically, we expect the blocking cations to be driven deeper into the pore toward the cavity. In correlating the crystallographic with electrophysiological data, it is most notable that the amino acids forming the Sr^{2+} sites in the crystal are the same amino acids that are known to affect blockage and rectification in electrophysiology experiments (*36*). Beyond providing a structural basis with which to explain past electrophysiological studies, the Kir2.2 structure also suggests many new experiments. For example, most studies on the mechanism of rectification have focused on electrostatic interactions between the positively charged blocker and negatively charged groups on the protein. But hydrophobic interactions between methylene groups of polyamine mole-

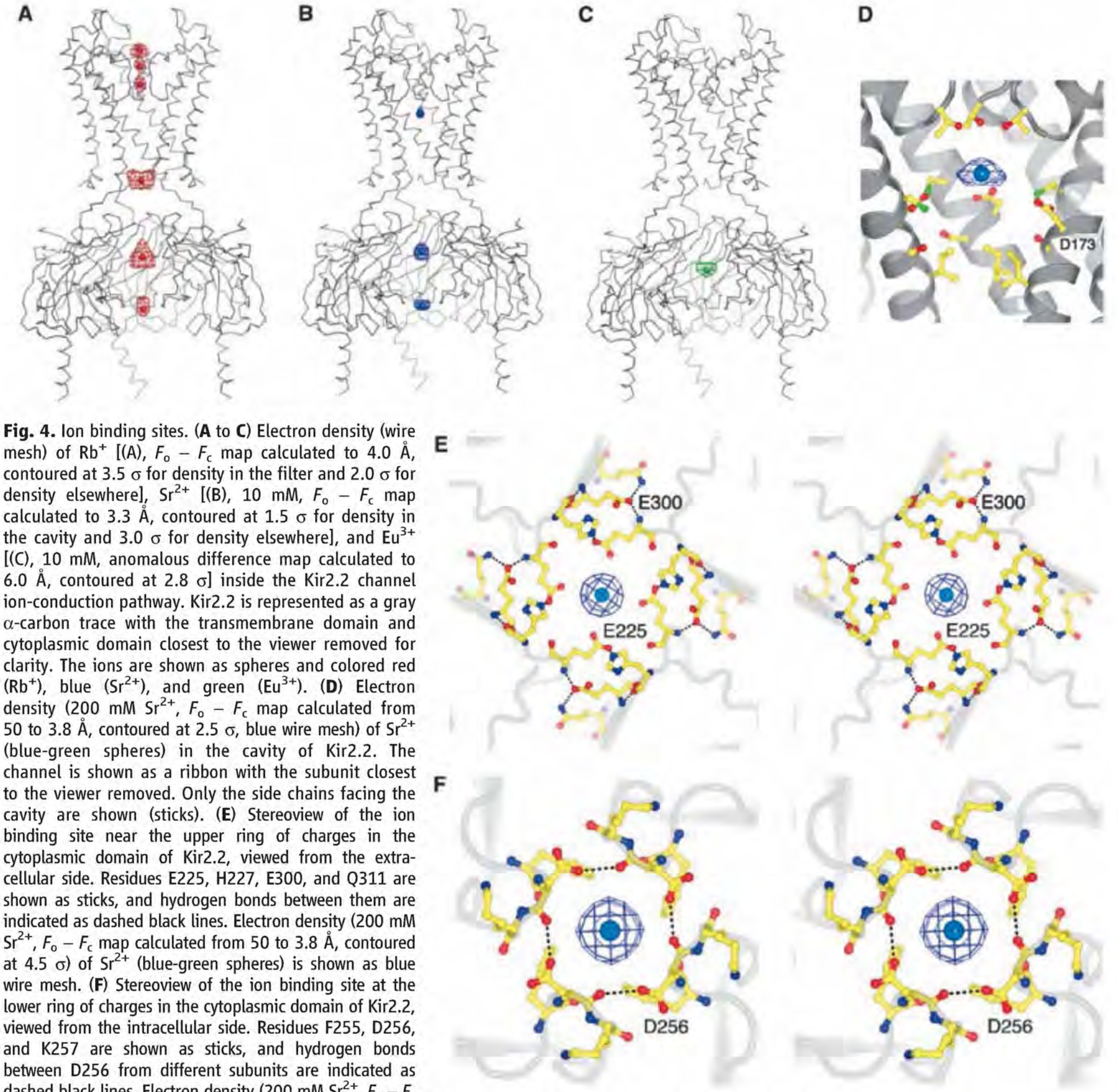


Fig. 4. Ion binding sites. (**A** to **C**) Electron density (wire mesh) of Rb^{+} [(A), $F_o - F_c$ map calculated to 4.0 Å, contoured at 3.5 σ for density in the filter and 2.0 σ for density elsewhere], Sr^{2+} [(B), 10 mM, $F_o - F_c$ map calculated to 3.3 Å, contoured at 1.5 σ for density in the cavity and 3.0 σ for density elsewhere], and Eu^{3+} [(C), 10 mM, anomalous difference map calculated to 6.0 Å, contoured at 2.8 σ] inside the Kir2.2 channel ion-conduction pathway. Kir2.2 is represented as a gray α-carbon trace with the transmembrane domain and cytoplasmic domain closest to the viewer removed for clarity. The ions are shown as spheres and colored red (Rb^{+}), blue (Sr^{2+}), and green (Eu^{3+}). (**D**) Electron density (200 mM Sr^{2+}, $F_o - F_c$ map calculated from 50 to 3.8 Å, contoured at 2.5 σ, blue wire mesh) of Sr^{2+} (blue-green spheres) in the cavity of Kir2.2. The channel is shown as a ribbon with the subunit closest to the viewer removed. Only the side chains facing the cavity are shown (sticks). (**E**) Stereoview of the ion binding site near the upper ring of charges in the cytoplasmic domain of Kir2.2, viewed from the extracellular side. Residues E225, H227, E300, and Q311 are shown as sticks, and hydrogen bonds between them are indicated as dashed black lines. Electron density (200 mM Sr^{2+}, $F_o - F_c$ map calculated from 50 to 3.8 Å, contoured at 4.5 σ) of Sr^{2+} (blue-green spheres) is shown as blue wire mesh. (**F**) Stereoview of the ion binding site at the lower ring of charges in the cytoplasmic domain of Kir2.2, viewed from the intracellular side. Residues F255, D256, and K257 are shown as sticks, and hydrogen bonds between D256 from different subunits are indicated as dashed black lines. Electron density (200 mM Sr^{2+}, $F_o - F_c$ map calculated from 50 to 3.8 Å, contoured at 4.5 σ) of Sr^{2+} (blue-green spheres) is shown as blue wire mesh.

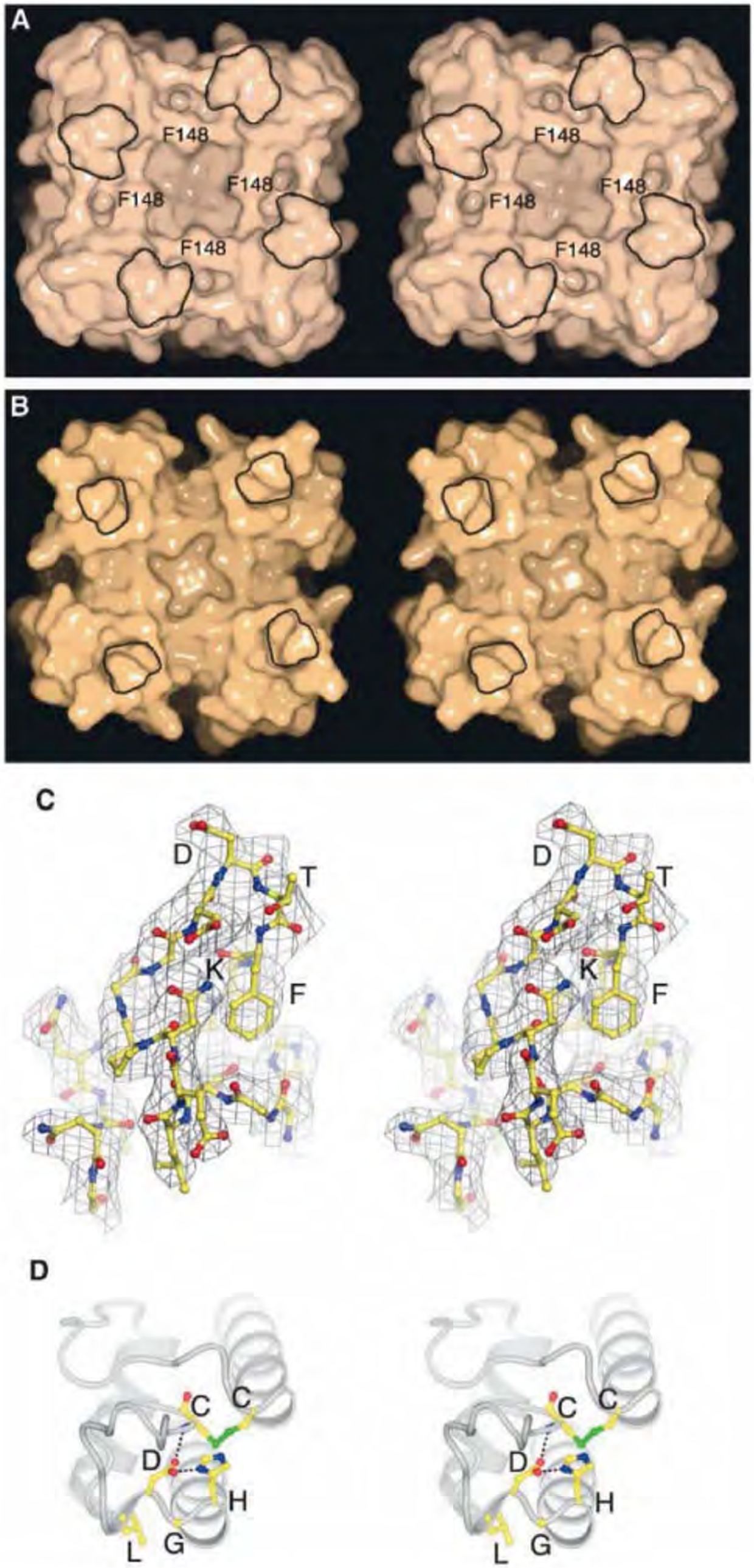


Fig. 5. Unique structure of the extracellular entryway. (**A** and **B**) Surface representation of chicken Kir2.2 (A) and Kv1.2-Kv2.1 paddle chimera [(B), PDB ID 2R9R] in stereo, viewed from the extracellular side. The four protrusions formed by the top of the turrets are highlighted with a black perimeter, and F148 in Kir2.2 is labeled. (**C**) Stereo representation of electron density (gray wire mesh) for the turret region ($2F_o - F_c$, calculated from 50 to 3.1 Å using phases from the final model and contoured at 1.0 σ). The turret is shown as sticks (colored according to atom types), and residues corresponding to the highlighted protrusions in (A) are labeled. (**D**) A close-up view of the turret region in a single subunit in stereo. Side chains of those conserved residues among the turrets of eukaryotic Kir channels, as well as C155, are shown as sticks. Hydrogen bonds between H108, D110, and C123 are indicated as dashed black lines.

cules and hydrophobic residues in the channel may be important. In particular, we might anticipate that when the pore opens, polyamines could interact strongly with the large hydrophobic amino acids at positions 177 and 181 when the leading amino group of the polyamine reaches into the central cavity (Fig. 3C) (*54*).

Since the earliest investigations of strong inward rectifiers, two important properties have been noted: a sharp transition from a conductive state to a nonconductive (blocked) state over a very narrow voltage range, and a dependence of the transition on the extracellular K^+ concentration (*60–63*). Specifically, the voltage at which the transition occurs shifts to more depolarizing values as extracellular K^+ concentration is increased. Both properties, the sharp transition (i.e., strong voltage dependence) and its dependence on extracellular K^+, have been attributed to the simple notion that conducting ions and blocking ions compete for sites in the pore (*12*, *52–57*, *64–66*). The crystallographic data presented here support this conclusion. We observe in the crystal Rb^+ binding at the same sites that can bind multivalent blocking ions. Therefore, a high extracellular K^+ (or Rb^+) concentration should favor occupation of the sites by conducting ions, and a more depolarizing voltage should be required to drive blocking ions into the pore from the cytoplasm to replace the conducting ions. Moreover, as blocking ions enter the pore from the intracellular side, the displaced conducting ions must move through the selectivity filter to the extracellular side; that is, movements of blocking and conducting ions must be coupled. Such coupling would have energetic consequences because movement of an ion across the membrane voltage difference constitutes work. Hence, a blocking ion entering the pore will exhibit a voltage dependence that results from a combination of its own charge and the charge of the displaced ions. This can be the origin of strong voltage-dependent block, which can be the origin of a biologically important property of strong rectifiers—their diode

property of a sharp transition from a conductive to a nonconductive state as a function of membrane voltage (*12*, *52–55*, *64*).

The extracellular pore entryway and pharmacology of Kir channels. Two aspects of the structure may account for the relative insensitivity of eukaryotic Kir channels, especially members of the Kir2 subfamily, to K^+ channel toxins (*22–24*). The turrets in Kir2.2 are larger and come closer together, constricting the pore entryway compared to Kv1.2; and F148 in the sequence TXGYGFR creates four protrusions on the surface at the pore opening (Fig. 5, A and B). Thus, in Kv channels, the entryway is wider and the pore opens onto intersecting grooves with a flat base, which form the docking surface for pore-blocking scorpion toxins (Fig. 5B). In Kir2.2, the entryway is constricted and the grooves are absent (Fig. 5A).

Though the shape of the eukaryotic Kir channel pore entryway might offer fewer opportunities for inhibitory protein-protein interactions, inhibition might occur by a somewhat different strategy. Inhibitors of Kir1.1 and Kir3.4 channels have been identified. A bee venom toxin, tertiapin, inhibits both of these channels (*22*). At 21 amino acids in length, tertiapin is smaller than most other venom toxins, so it might fit between the turrets more effectively. Alternatively, the turrets themselves might form the binding site for tertiapin (*67–69*). At 57 amino acids, δ-dendrotoxin from the green mamba snake is rather large, and yet it inhibits Kir1.1 channels (*23*). Compared to tertiapin, less is known about the binding site on the channel for δ-dendrotoxin, but one aspect of its inhibition is intriguing: The blocked state reduces single-channel conductance to about 10% rather than inhibiting it completely. δ-Dendrotoxin most likely binds to the turrets but is too large to fit tightly over the pore, which would imply that binding to the turret may be sufficient to alter the channel's function.

The idea that binding to the turrets could alter function is not surprising when one considers that the turret in Kir2.2 is not a loop, but forms a highly ordered structure (Fig. 5C). The base of the turret is formed and pinned together by the HGDL sequence, which with only minor variation is found in all eukaryotic Kir channels (Figs. 1 and 5D). H108 stabilizes D110 through a hydrogen bond. The Asp (D) itself is hydrogen bonded to the amide nitrogen of C123, which effectively holds the two ends of the turret together. L111 projects from the surface of a short 3_{10} helix into the protein interior to make stabilizing hydrophobic interactions. Thus, the turrets are structurally important elements of the channel. Between the sequence HGDL and the first Cys of the disulfide bridge, the turret sequence is highly variable among Kir channel subtypes. The Kir2.1 channel becomes sensitive to tertiapin if the variable sequence is mutated to be Kir3.4-like (*68*). Therefore, the turrets appear to be structures through which specific inhibition of Kir channel subtypes might be achievable through directed evolution of specific protein binding partners.

Summary. This paper presents the atomic structure of a eukaryotic Kir channel, Kir2.2, a strong inward rectifier. The sequence TXGYGFR gives rise to a K^+ selectivity filter stabilized by disulfide bridges and salt bridges that distinguish eukaryotic Kir channels. Multiple ion binding sites on the intracellular side of the selectivity filter can be occupied by conducting ions but exhibit higher affinity for multivalent blocking ions. Thus, blocking ions entering from the cytoplasm must displace conducting ions through the pore. This situation is expected to give rise to strong voltage-dependent block and diode-like conduction properties. Structural features of the extracellular pore entryway offer an explanation for the relative insensitivity of Kir channels to venomous toxins and a possible approach to the development of selective Kir channel inhibitors.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/326/5960/1668/DC1
Materials and Methods
Figs. S1 to S3
Table S1
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Formation and Survival of Water Vapor in the Terrestrial Planet–Forming Region

Thomas Bethell* and Edwin Bergin

Recent astronomical observations have revealed what may prove to be the ubiquity of water vapor during the early stages of planet formation. We present here a simple mechanism showing how water vapor forms in situ and is capable of shielding itself from molecule-destroying stellar radiation. The absorption of this radiation by water can control the thermodynamics of the terrestrial planet–forming zone. Similar to Earth's ozone layer, which shelters the chemistry of life, the water layer protects other water molecules and allows for a rich organic chemistry. The total abundance of water vapor in the natal habitable zone is equal to that of several thousand oceans.

The initial steps of planet formation in both the solar nebula and extrasolar planet-forming disks are believed to involve the growth of submicrometer dust grains and their subsequent settling from the upper layers toward the dust-rich disk midplane. A key facet of this process is that as grains grow to larger and larger sizes, the accompanying attenuation of molecule-destroying energetic radiation is reduced (*1*). This should eventually lead to the increased destruction of water vapor in the terrestrial planet–forming region at 1 astronomical unit (AU).

Over the past decade, astronomical observations have revealed the presence of water and OH vapor in the disks around young stars [for example, (*2*)]. The observed conditions of these systems are consistent with the expectation that water resides in the gas, forming via high-temperature chemical reactions or from the evaporation of icy planetesimals. These conditions illustrate that water is prevalent in these systems, at least in the warm upper layers of the circumstellar disk.

Recent observations made with the Spitzer Space Telescope (*3*, *4*) show that the inferred water-column density varies by only a factor of 5 across a sample of three protoplanetary disks: $N(H_2O) \equiv \int n(H_2O)dz \sim 1.6 \times 10^{17}$ to 8×10^{17} cm^{-2}, where N is the column density (cm^{-2}), n is the volumetric density (cm^{-3}), and z is the height above the disk midplane (cm) (Table 1). Given that the far-ultraviolet (FUV, wavelength ~ 91.2 to 200 nm) absorption cross-section of H_2O (and OH) is $\sigma_{H_2O} \sim \sigma_{OH} \sim 5 \times 10^{-18}$ cm^2 (*5*, *6*), the FUV optical depth τ of both water and OH in these disks is on the order of unity ($\tau = \sigma N \sim$ few). When τ exceeds unity, the participating medium impedes the propagation of radiation. Is it possible that the propagation of energetic photons in these systems is not simply coupled to but is actually controlled by the onset of water formation? This idea represents a shift in our assumptions about the survival mechanisms of molecules in dense interstellar gas bathed by energetic photons, where solid grains are generally assumed to provide most of the shielding. In fact, in the absence of dust shielding, an exposed circumstellar water molecule would normally be destroyed in only a few seconds. Under typical galactic interstellar conditions, molecules are never sufficiently abundant to compete with dust opacity. In contrast, we show here that during the early stages of planet formation, when grains have grown and settled sufficiently, the rapid formation of water and OH allows these molecules to be the dominant absorbers of UV radiation.

The gas-phase production of water in H_2-dominated disks is believed to follow a simple reaction sequence that is characterized by forward kinetic reactions and backward photolytic reactions

$$O \underset{UV}{\overset{H_2}{\rightleftharpoons}} OH \underset{UV}{\overset{H_2}{\rightleftharpoons}} H_2O \qquad (1)$$

For the forward reactions to be most efficient, the gas temperature should exceed 300 K (Fig. 1) (*7*, *8*), whereas the backward photolytic reactions are driven by UV photons in the wavelength range from 110 to 180 nm (*5*, *6*). The chemical processing of the disk material depends primarily on the local density of stellar photons, the gas temperature, and the gas density (*9*). At the densities of interest ($n_H \geq 10^8$ cm^{-3}), chemical time scales are on the order of minutes, much shorter than the time scales for transport processes (*9*, *10*). Thus, the chemistry rapidly reaches its steady-state conditions, and the molecular fractions f of water and OH may be expressed as

$$f_{H_2O} = \frac{\rho^2 K}{\rho^2 K + \rho K + 1} f_{O_{tot}} \text{ and}$$
$$f_{OH} = f_{H_2O}/\rho \qquad (2)$$

The molecular fractions are expressed as a fraction of the total available oxygen fraction $f_{O_{tot}}$ (defined as the abundance of oxygen nuclei not in CO relative to that of hydrogen, $f_{O_{tot}} \sim 2 \times 10^{-4}$ for solar abundances) (*11*). The temperature parameter $K = k_{H_2O}/k_{OH}$, where k indicates a two-body rate coefficient, quantifies the relative strengths of the forward reactions $O + H_2 \xrightarrow{k_{OH}} OH$ and $O + H_2 \xrightarrow{k_{H_2O}} H_2O$. As such, it increases rapidly with gas temperature T, reflecting the fact that the gas-phase production of water proceeds vigorously above $T \sim 300$ K. The density parameter $\rho = k_{H_2O} n_H / \sigma_{H_2O} n_{ph}$ expresses the competition between two-body forward reactions and the backward reactions caused by the destruction of molecules by ambient UV photons with density n_{ph}. In the context of a protoplanetary disk, both n_H and n_{ph} will vary considerably with height above the disk midplane.

Examining Eq. 2 reveals the following criterion determining when water is the dominant oxygen-bearing species

$$2\rho - 1 \geq \sqrt{1 + \frac{4}{K}} \qquad (3)$$

When this criterion is met, then the disk is "wet" (that is, H_2O is the dominant carrier of oxygen); otherwise, it is "dry" (that is, atomic oxygen is the dominant form). The criterion is

Table 1. A summary of the system properties and observed abundances of warm water and OH vapor within the inner ~3 AU of three protoplanetary disks (*2*, *3*). We also show the column densities predicted by our self-shielding model. The total column density of oxygen-bearing species is used as a proxy for the hydrogen column, $N_H \geq (N(CO)+N(H_2O)+N(OH))/4 \times 10^{-4}$. Column densities in the table are integrated vertically, corrected for inclination, and must be multiplied by 10^{17} cm^{-2}. $\dot{M}_{acc}$, stellar mass accretion rate; $M_\odot$, solar mass.

Properties	Protoplanetary disks		
	DR Tau	AS 205A	AA Tau
$\dot{M}_{acc}$ (10^{-7} $M_\odot$ year^{-1})	0.32 to 79	7.2	0.07
N(CO)	70 ± 2.1	60 ± 1.8	1.3 ± 0.4
T(K)	1000 ± 150	1000 ± 150	550 ± 75
Observed $N(H_2O)$	8 ± 2.4	6 ± 1.8	1.6 ± 0.6
Predicted $N(H_2O)$	~10	~10	~1
Observed N(OH)	2 ± 0.6	2 ± 0.6	0.2 ± 0.1
Predicted N(OH)	~2	~2	~0.1

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largely a function of the (photon and gas) density and temperature. In general, high temperatures (increasing K) and dense gas and weak radiation fields (increasing ρ) drive the chemistry toward water formation.

The vertical density structure of a circumstellar disk in hydrostatic equilibrium is such that most of the mass resides in the midplane, above which lies a spatially extended atmosphere (*12*, *13*). The settling of dust toward the disk midplane that occurs in the early stages of planet formation (*14*) greatly reduces the opacity in the upper layers, making these parts of the disk more transparent (*1*). Analysis of Spitzer Space Telescope data suggests that the dust abundance in the disk surface layers is reduced to <1% of its primordial (interstellar) value in the majority of nearby young stars, including those described in this report (*15*). Under these transparent conditions, the chemistry in the exposed layers would normally be limited to only those species that are capable of shielding themselves efficiently from radiation: the two molecules CO and H_2 (*16*). However, once the local dust abundance is reduced to <1% of its primordial value, the combined opacity of incipient water and OH becomes the dominant factor controlling the propagation of energetic photons, $\tau \rightarrow \tau_{H_2O} + \tau_{OH} = \sigma_{H_2O}N(H_2O) + \sigma_{OH}N(OH)$. In this regime, the accumulation of water and OH drives a precipitous decline in photon density, accompanied by a rapid increase in the water fraction (Eqs. 2 and 3). This runaway feedback process is the self-shielding mechanism. Regardless of whether self-shielding is instigated by water or OH, the outcome is always the same: the total conversion of available oxygen into water. It is also this mechanism that limits the maximum OH column density to $N(OH) \leq 2 \times 10^{17}$ cm^{-2} (corresponding to $\tau_{OH} \leq 1$), exactly as observed (Table 1). The chemistry dictates that water formation ultimately comes at the expense of OH. An important consequence of the absorption of stellar radiation by water in the disk atmosphere is that it aids water vapor formation closer to the cold disk midplane (Fig. 1), where most of the mass resides and where planets are born.

Quantitative model predictions for the column densities of warm OH and water are shown in Fig. 2, covering a range of disk models parameterized by gas temperature T, column density of the warm layer N_H, and accretion luminosity L_{FUV} of the central star (*9*). Situating the observed disks in this parameter space is difficult because of the uncertainty and intrinsic variability in the properties of these objects. Nevertheless, there is a general agreement between observations and predictions (Table 1). The plateau in $N(OH)$ seen in Fig. 2 is a key signature of self-shielding.

Models of disk gas thermodynamics are important for understanding the physics of gas in the planet-forming zone, as well as for revealing observational tracers of these regions. These models generally assume that warm layers will exist deeper into the disk as the dust grains settle

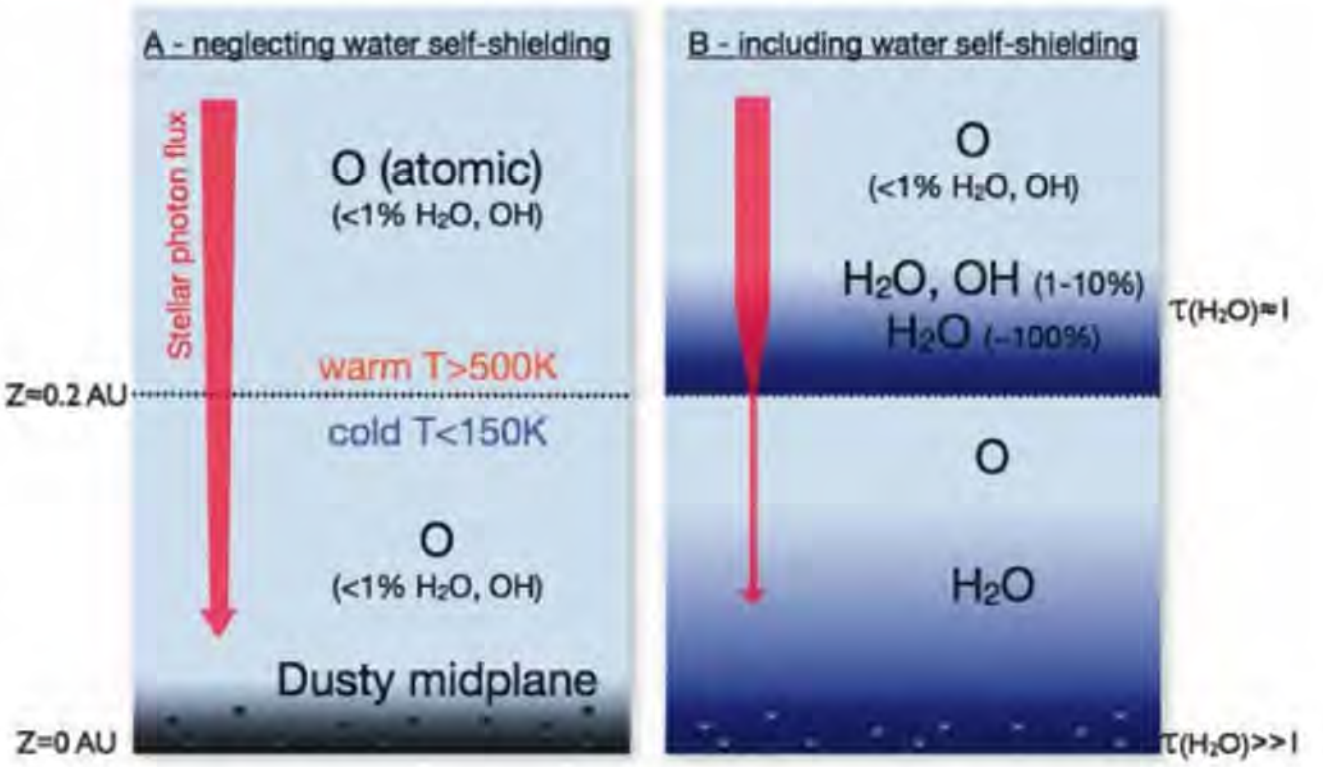

Fig. 1. Cartoon illustrating the water self-shielding mechanism and the resulting vertical chemical stratification. In a disk in which dust has largely settled to the midplane (for example, AA Tau), the neglect of water self-shielding (**A**) leads erroneously to a situation of predominantly atomic oxygen through most of the vertical extent of the disk. In the warm layer, both water and OH are present in small amounts because of pervasive photodissociation by UV photons that are largely unimpeded by the low levels of dust present. There is also very little water near the cold dense midplane, where slow formation rates cannot compete with residual photodissociation. In contrast, considering water self-shielding (**B**) leads to a "wet" warm layer. Here the (volume-averaged) efficiency of water formation increases from <1% to >10%, which is consistent with observations. The regions of abundant OH are limited by the runaway formation of water, a signature of the self-shielding mechanism. There is widespread formation of water in the cold disk, shielded by both the overlying warm and cold water. The amount of cold atomic oxygen in this region drops with an increase in the abundance of warm water (for example, DR Tau and AS 205A).

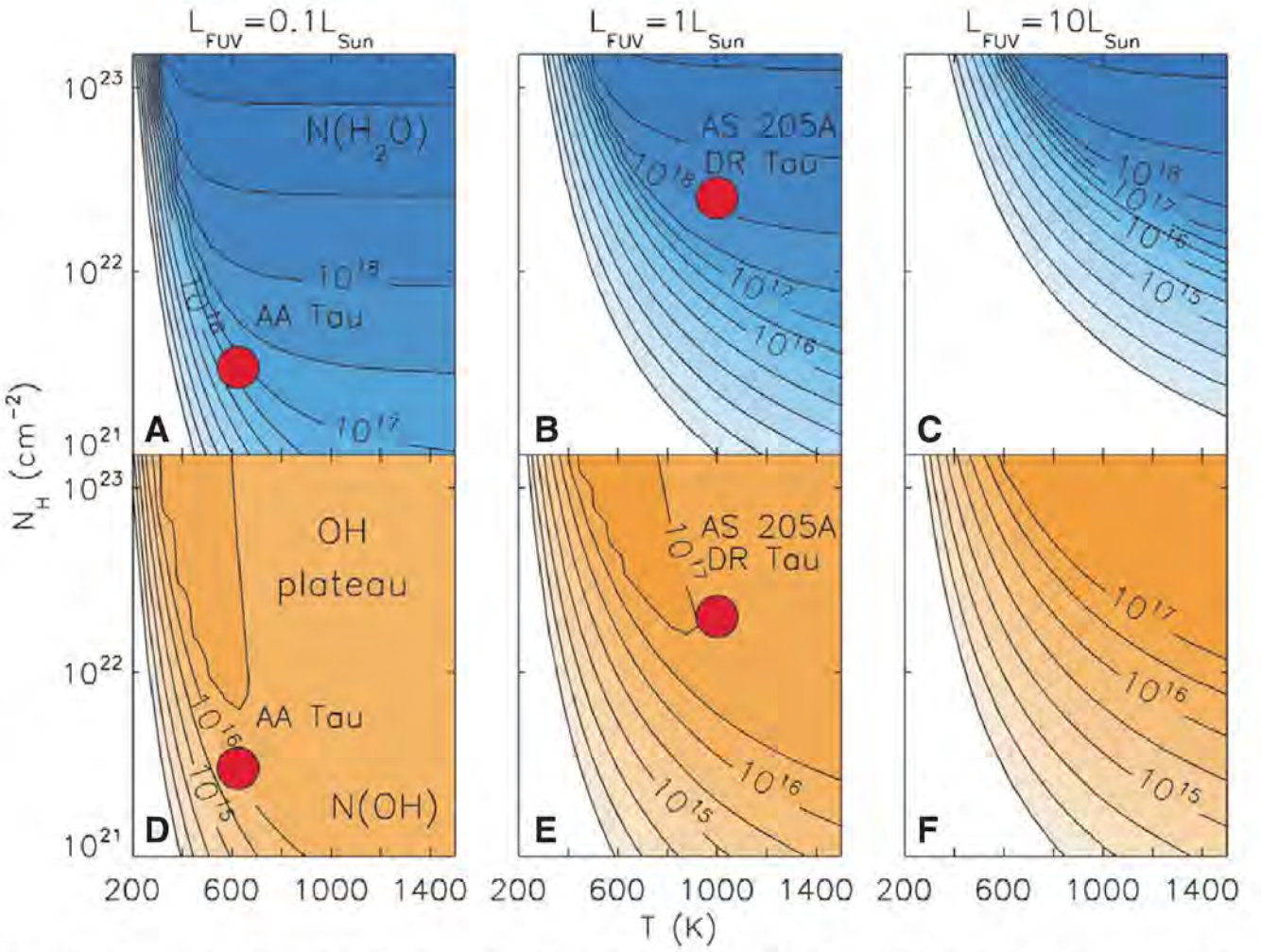

Fig. 2. Observed and predicted column densities of warm water (**A** to **C**) and OH (**D** to **F**). The contours in (A) and (D) are model predictions for the water and OH column densities in a disk illuminated by a star with a modest $L_{FUV} = 4 \times 10^{32}$ erg s^{-1}, consistent with the system AA Tau (*2*). Similarly, (B) and (E) depict the results for $L_{FUV} = 4 \times 10^{33}$ erg s^{-1}, consistent with the more luminous systems AS 205A and DR Tau (*3*). The predictions of (C) and (F) are appropriate for highly luminous systems, $L_{FUV} = 4 \times 10^{34}$ erg s^{-1}. Contours are spaced logarithmically. Specific model predictions for the three systems are included in Table 1.

to the midplane (*17*). However, for wet disks, the energetic photons that normally heat the disk via photoelectric heating are now also absorbed by H_2O in the dust-poor atmosphere. This changes the characteristics of the gas and dust heating; the primary heating agents can now be the hot photoproducts of the photodissociated water (OH, O, and H). Laboratory experiments and theoretical modeling of photoexcited water suggest that as much as 50 to 70% of the photon energy will be deposited locally in the disk atmosphere as heat (*18*). The remainder is radiated by highly rotationally excited and superthermal OH in its ground electronic state at wavelengths between 10 and 30 μm (*19*). This line radiation provides a nonlocal source of heating deeper in the disk, perhaps down into the planet-forming zone. Furthermore, in disks for which FUV radiation is the principal gas-heating agent, the buildup of a sufficiently large column density of water will be the main factor limiting the extent of the warm layer. Thus, in disks where the thermodynamics are strongly coupled to the water chemistry, the onset of water self-shielding will truncate the warm layer at a depth corresponding to $\tau_{H_2O} \cong$ few. A limit is therefore imposed on the column density of warm water; in effect, the water becomes a victim of its own success. Despite this effect, the cold water near the midplane will still be shielded and may even initiate its own vigorous self-shielding. The observations are consistent with this possibility (warm $\tau_{H_2O} \leq$ few), although the precise roles played by the main disk-heating agents (for example, FUV and x-rays) are still largely unknown (*20*). Recently, water formation has been independently examined in an x-ray–dominated disk with no FUV (*21*). Those models can produce the observed water column densities, but they are deficient in OH. Our water self-shielding mechanism is able to match both. Even in dust-rich disks, water can provide an additional source of UV opacity and contribute to disk heating.

The persistence of water vapor in our models suggests that it is unlikely to be a transient phenomenon and may be present during the era of planet formation. It also shows that gaseous water vapor originating from evaporating icy planetesimals (*22*, *23*) is not the sole mechanism that can match astronomical observations. Similar to the ozone layer that protects Earth's surface from the destructive effects of solar UV radiation, water created in situ at the disk surface within a few astronomical units of the star will protect any water vapor either created via gas-phase reactions or supplied to the midplane via evaporating icy planetesimals. In addition, the surface water will protect any molecules created by gas-phase chemistry, allowing for a rich organic chemistry to persist in the inner few astronomical units, even as the dust grains evolve toward planets (*3*, *24*). Some of this water and organic material could potentially be incorporated into nascent Earth-like worlds (*25*, *26*).

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Supporting Online Material

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Spatial Organization of Hominin Activities at Gesher Benot Ya'aqov, Israel

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The spatial designation of discrete areas for different activities reflects formalized conceptualization of a living space. The results of spatial analyses of a Middle Pleistocene Acheulian archaeological horizon (about 750,000 years ago) at Gesher Benot Ya'aqov, Israel, indicate that hominins differentiated their activities (stone knapping, tool use, floral and faunal processing and consumption) across space. These were organized in two main areas, including multiple activities around a hearth. The diversity of human activities and the distinctive patterning with which they are organized implies advanced organizational skills of the Gesher Benot Ya'aqov hominins.

Ethnographic data of modern hunter-gatherers suggest that their activities are spatially patterned (*1*). Accordingly, the organization of activities across space is often associated with modern humans and is thus considered to reflect modern behavior (*2*, *3*). Attempts to trace the origins of this behavior have concentrated on spatial analyses of Middle Stone Age/Middle Paleolithic sites in Africa (*3*), Europe (*4*), and the Levant (*5*, *6*). Spatial analyses of archaeological sites offer insight into past human activities, behavior, and cognition and provide evidence of how hominins perceived their living space, functionally and/or socially. Here, we present a spatial analysis of an Acheulian occupational level from

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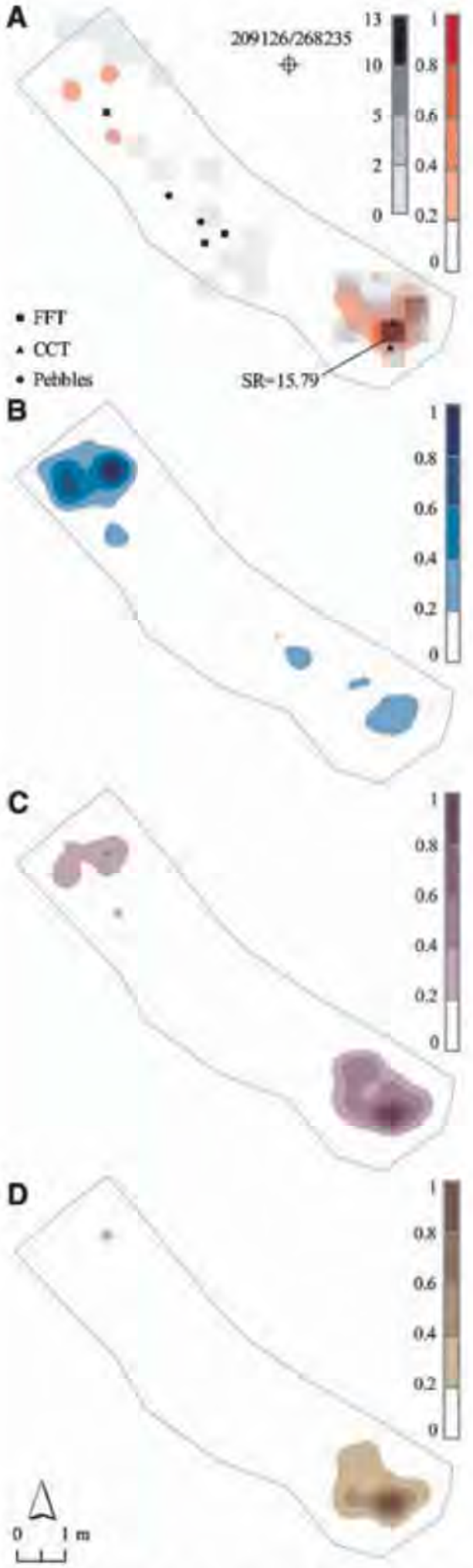

Fig. 1. Kernel density maps of microartifacts in Level 2. (**A**) Burned flint microartifacts (N = 563). Shown are excavated units in which the observed percentage of burned microartifacts exceeds the expected percentage (gray-to-black scale); significant Standardized Residuals (SR) values (*17*); and the distribution of large burned flint items [flakes and flake tools (FFT), N = 3; cores and core tools (CCT), N = 2; pebbles, N = 2]. (**B**) Unburned flint microartifacts (N = 73,064). (**C**) Basalt microartifacts (N = 3889). (**D**) Limestone microartifacts (N = 2154). (A map reference to the Israel Grid, coordinates to the nearest meter, appears at the top of all figures.)

Gesher Benot Ya'aqov, which shows that some early humans were organizing their living spaces by 790,000 years ago.

Gesher Benot Ya'aqov is located on the shores of the paleo–Lake Hula in the northern Jordan Valley in the Dead Sea Rift (*7*). The Early to Middle Pleistocene sediments document an oscillating freshwater lake and represent some 100,000 years of hominin occupation (Oxygen Isotope Stages 18–20) dating to 790,000 years ago (*8*, *9*). Fourteen archaeological horizons indicate that Acheulian hominins repeatedly occupied the lake margins, where they skillfully produced stone tools, systematically butchered and exploited animals, gathered plant food, and controlled fire (*7*, *10*–*15*).

We focus on a hearth area and the lithic, botanical, and paleontological assemblages of Layer II-6 Level 2 (henceforth Level 2), one of eight superimposed occupational levels in Layer II-6. This sedimentary sequence was rapidly sealed, preserving the original location of different artifacts (evidenced by the fresh preservation state of the lithics, the preservation of mollusk embryos, the presence of conjoinable bones, and a lack of winnowing) (*8*, *10*, *15*, *16*). Level 2 is 0.12 m thick, and we excavated across an area of 25.6 m^2 (3 m^3). It yielded numerous stone artifacts made of different raw materials; a large assemblage of wood, bark, fruits, seeds, and nuts; and highly diverse lacustrine and terrestrial animal remains.

Phantom hearths could be identified by the spatial distribution of small burned debris (*15*). The flint items from Level 2 exhibit low frequencies of burning (table S1): only 0.76% of the microartifacts and 1.05% of the macroartifacts (*17*). Although unburned flint microartifacts occur mostly in the northwestern area, most of the burned ones are concentrated in 3.25 m^2 in the southeast (Fig. 1 and fig. S1). Close to 60% of the burned flint microartifacts, but only 22% of the unburned ones, occur within this limited area (*17*).

The concentration of burned flint microartifacts reflects a knapping activity area near a hearth. A variety of parameters (*15*) support the interpretation of an anthropogenic fire rather than a natural one. In addition, wood segments in Level 2 are abundant but rarely burned: Only two (2.63%

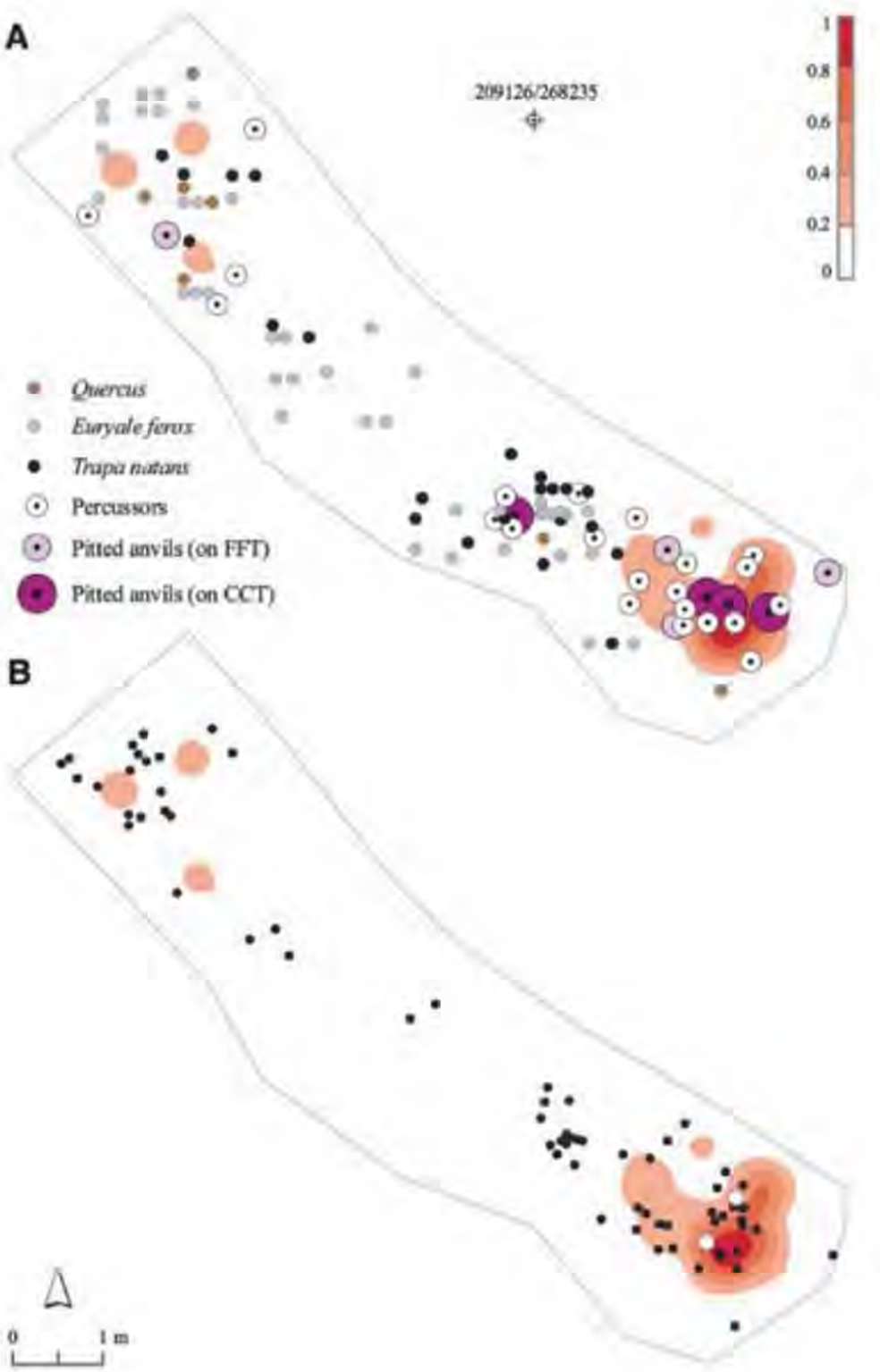

Fig. 2. (**A**) The distribution of pitted stones (N = 8), percussors (N = 22), and *Euryale ferox* (N = 41), *Trapa natans* (N = 22), and *Quercus* (N = 7) nuts in Level 2, superimposed on the kernel density map of burned flint microartifacts (N = 563). (**B**) Distribution of wood pieces (N = 74); the two burned pieces are marked in white.

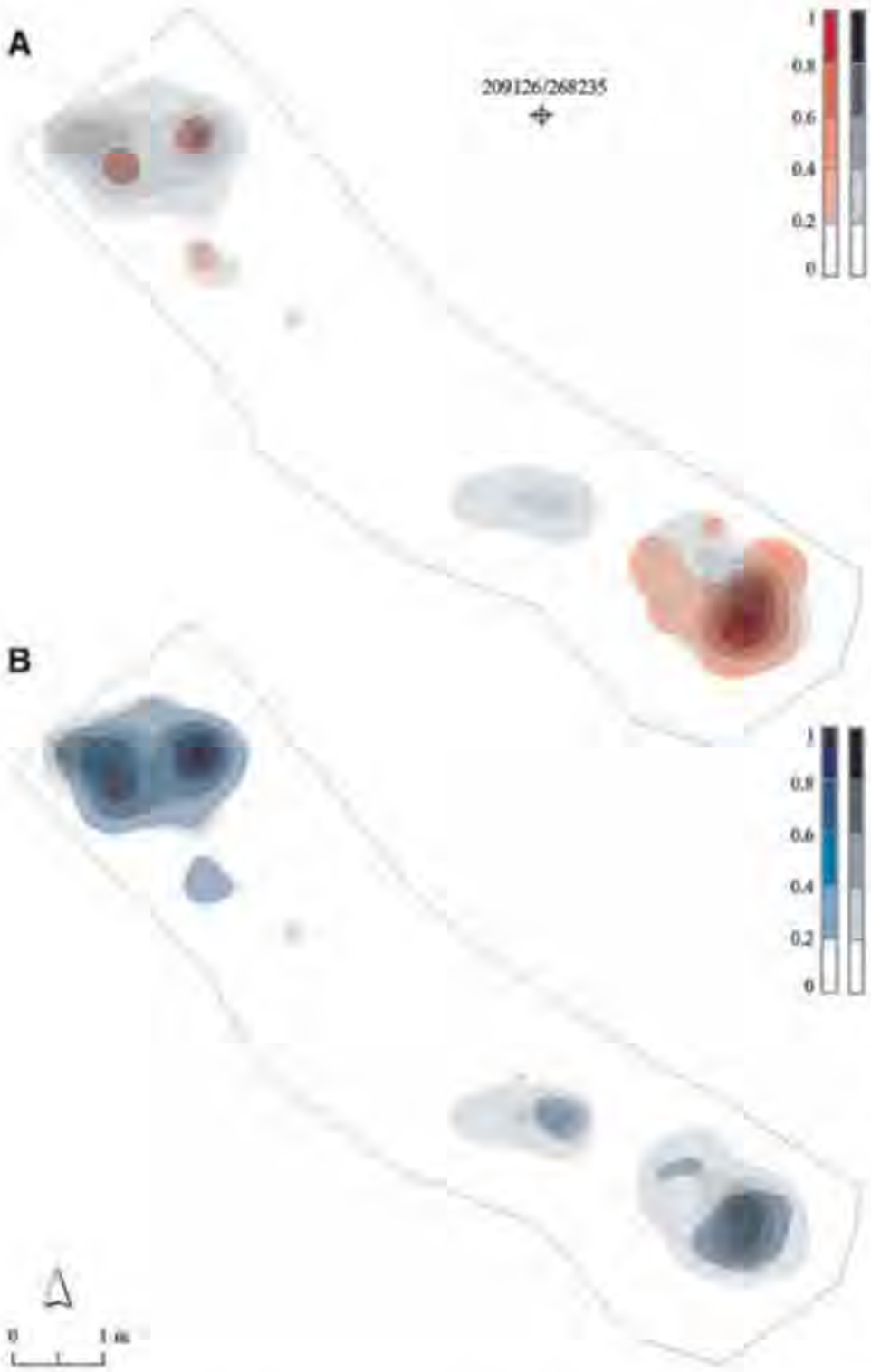

Fig. 3. Kernel density map of the distribution of fish remains (N = 2457) in Level 2, slightly transparent and superimposed on the kernel density map of (**A**) burned flint microartifacts; (**B**) unburned flint microartifacts.

of the wood assemblage), in spatial association with the hearth area, are burned (Fig. 2). Among the smaller botanical remains (grains, fruits, seeds, and wood pieces smaller than 2 cm), burning frequencies are 3.4% (8 of 238). Low frequencies of burning are also recorded for the different flint artifacts (table S1). Burning of flint artifacts at Gesher Benot Ya'aqov required a high temperature (above 350°C) and direct contact with the flints (*18*, *19*).

The lithic assemblage of Level 2 comprises 79,670 microartifacts and 1412 macroartifacts (table S1). Kernel density maps of flint, basalt, and limestone microartifacts reveal that flint knapping was carried out mostly in the northwestern area and, to some extent, near the hearth (Fig. 1 and fig. S1). In contrast, basalt and limestone are concentrated in the southeastern area (Fig. 1 and fig. S1). Several bifaces were recovered close to the hearth and most were some 2 m to the northwest (fig. S2). Soft hammer knapping, often linked with biface production (*20*), also seems to be associated with the hearth area, as evidenced by the typical traits observed on basalt and flint flakes (e.g., lipped striking platforms) (*21*), most of which occur close to the hearth (fig. S2).

Some tool types (e.g., notches and denticulates) were distributed throughout the excavated area, but others were most abundant within 1 m of the hearth (fig. S3 and table S2). Several basalt and limestone artifacts bear pits of various quantities, sizes, and depths, interpreted as resulting from the recurrent cracking of hard nuts (*12*). Seven of the eight pitted stones occur near the hearth (Fig. 2). A similar distribution is observed for percussors (hammerstones): 18 of 22 are located near the hearth (Fig. 2).

The botanical assemblage (table S3) comprises 61 wood fragments (larger than 2 cm) and 13 pieces of bark. Thirteen wood taxa are identified, including Syrian ash (*Fraxinus syriaca*), olive (*Olea europaea*), and Kermes oak (*Quercus calliprinos*). More than 200 seeds and fruits represent 19 different taxa. Although most taxa indicate wet habitats (e.g., lakes, lake margins, swamps, and near streams), the abundant fruit remains of woodland species such as olive, oak, and officinal storax (*Styrax officinalis*) imply human involvement, as their habitat was likely located some distance from the lake shore. Edible plants include oak acorns, prickly water lily (*Euryale ferox*) seeds, and water chestnut (*Trapa natans*) fruits; these were probably staple foods because of the nutritive value of their starchy nuts. Through roasting, the inedible shell of the nuts can easily be peeled and the tannin content of the acorns reduced. The fruits of the wild grapevine (*Vitis sylvestris*) and olive, and the leaves of the white beet (*Beta vulgaris*) and holy thistle (*Silybum marianum*), may also have been consumed. Because of their low specific gravity and the proximity of the occupations to water, plant pieces smaller than 20 mm (i.e., seeds and fruits) cannot serve as a reliable spatial indicator. Most wood pieces were near the hearth, and the two burned specimens were located within it (Fig. 2).

We recovered remains of various aquatic and terrestrial species (tables S4 and S5). The 17 crab specimens [minimum number of individuals (MNI) = 4 (*22*)], identified as the extant *Potamon potamios*, include pieces of the two asymmetric chelipeds, each with a distinctive form of the movable (upper) and fixed (lower) pincer. Pincers, being thicker and denser than other body parts, constitute 76.5% of the assemblage (table S4). Five display features that permit estimation of the carapace height (*22*) as 23.0 to 48.8 mm, characteristic of medium- and large-sized crabs. Of the seven pincers of the large cheliped present in Level 2, six occur around the hearth. These are the only crab remains in this area (fig. S4) (*23*).

The abundant fish remains [number of identified specimens (NISP) > 2500] (table S5) include three of the five freshwater fish families native to Lake Hula (*24*, *25*). Cyprinidae (carps) predominate (99%) with five identified species, including endemic species (e.g., *Mirogrex hulensis*). Most (62.1%; N = 1602) consist of the extinct large (longer than 1 m) *Barbus* sp. nov. The preservation of fish bones is poor, exhibiting a preponderance of molariform and pharyngeal teeth (99%) and a paucity of other skeletal elements (16 identified skeletal elements out of the more than 70 bones of a complete fish) (table S6). Most of the molariform teeth (>80%) and the fin spines (>60%) are highly fragmented, with less than 40% of the original element present. The fish remains are clumped [Morisita Index of Dispersion; I_d = 3.5, M_u = 0.99, M_c = 1.0071, I_p = 0.5292; see (*17*)] in two concentrations: one in the northwest and one in the southeast, where the hearth is located (Fig. 3). Considering the significant difference between the Level 2 fish assemblage and that of a natural-death assemblage (*26*, *27*) (table S7; χ^2 by randomization: df = 20, χ^2 = 1878.797, $P < 0.0001$), we conclude that the fish assemblage of Level 2 is of anthropogenic origin, demonstrating that this resource was another component of the hominin dietary spectrum. These conclusions are strengthened by the spatial distribution of fish remains, which overlap the activity areas illustrated by the lithics (Fig. 3).

Other faunal remains include freshwater turtles (*28*) and medium- and large-sized mammals (fig.

S4). The latter ($N = 27$) comprise fallow deer, elephant, and bone fragments assigned to general categories (e.g., artiodactyls, canids, and unidentified mammals). Rodent teeth ($N = 22$) were also recovered, mainly of *Microtus* (table S4). The mammals' spatial distribution reveals no distinct patterns (fig. S4).

Analyses of Level 2 indicate that hominins carried out different activities in two distinct locations. Abundant flint knapping took place in the northwestern area, resulting in a dense concentration of microartifacts (Fig. 1 and fig. S1). Other noteworthy aspects of this activity area include fish exploitation (Fig. 3) and the use of chopping tools (fig. S3).

Greater variation was seen in the activities carried out near the hearth. Although flint knapping around the hearth was less intensive, basalt and limestone knapping was spatially restricted to the hearth (Fig. 1 and fig. S1). The hearth area also served as a focal point for biface modification and for activities involving the use of chopping tools, side scrapers, end scrapers, and awls (fig. S3). The percussors and the pitted stones suggest that nut processing may have involved the use of fire, as recorded for modern hunter-gatherer societies (*1*, *29*). In addition, the differential preservation of fish and crabs, along with their spatial distribution, suggests that they were consumed near the hearth.

The spatial organization of hominin activities in Level 2 thus resulted in discrete patterning of various categories of finds. The evidence from Gesher Benot Ya'aqov suggests that early Middle Pleistocene hominins carried out different activities at discrete locations. The designation of different areas for different activities indicates a formalized conceptualization of living space, often considered to reflect sophisticated cognition and thought to be unique to *Homo sapiens* (*3*). Modern use of space requires social organization and communication between group members, and is thought to involve kinship, gender, age, status, and skill (*2*).

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Mozambican Grass Seed Consumption During the Middle Stone Age

Julio Mercader

The role of starchy plants in early hominin diets and when the culinary processing of starches began have been difficult to track archaeologically. Seed collecting is conventionally perceived to have been an irrelevant activity among the Pleistocene foragers of southern Africa, on the grounds of both technological difficulty in the processing of grains and the belief that roots, fruits, and nuts, not cereals, were the basis for subsistence for the past 100,000 years and further back in time. A large assemblage of starch granules has been retrieved from the surfaces of Middle Stone Age stone tools from Mozambique, showing that early *Homo sapiens* relied on grass seeds starting at least 105,000 years ago, including those of sorghum grasses.

The Mozambican cave site of Ngalue (12°51.517′S, 35°11.902′E) is part of the Niassa Rift (Fig. 1). The cave formed in Proterozoic carbonate rocks (*1*) located at 1300 m above sea level. There is a 20-m-long corridor leading into dark chambers, which have the most habitable space, with a useable floor area covering >50 m^2 and a ceiling height of ~8 m. The portion of the sequence and the artifacts studied here were deposited throughout the so-called "Middle Beds" (*2*), a Middle Stone Age clast-supported and time-averaged unit with light yellowish brown sediments that are rich in angular cave spall, lithics, animal bones, and teeth. The deposits span a time range from 105,000 to 42,000 years ago (*2*). Excavation in 2007 retrieved 555 quartz artifacts.

For this study, I chose 70 stone tools (~12% of the Middle Stone Age assemblage) from all main technotypological types to take into account the broadest range of potential plant uses: scrapers (35%), core tools/grinders (25%), points (15%), flakes (7%), and miscellaneous tools (18%) (Table 1). I selected tools from across the entire industrial scatter across a 13-m transect running along the largest cave chamber. These include

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cobble-sized core implements that have the right size and weight to be used as grinders of vegetable material: Cores and core scrapers make up more than one-third of the entire assemblage. Special pieces include a rhyolite grinder/core axe, a ground cobble, and a faceted quartz mortar. The last two implements were flaked on one side to create a dish. All three appear to be covered with red or orange pigments, and in one case there is a patina over the ochre. The lithics have a mean mass of ~85 g (range, <1 to 1000 g) and maximum length of ~50 mm (Table 1). About 20% lack any starch residue (n = 12 stone tools), but 80% have some. In all, 2369 granules were identified on these, and each tool on average has 41 granules (range, 1 to 654). The average number of grains on lithics is 270 times larger than that in the site's free-standing sediments. Moreover, the mean number of granule types on stone tools is about 125 times the number of classified morphotypes retrieved from modern topsoils outside the cave. Three-fourths of the starch grains come from scrapers (50.5% of the total) and core/grinding tools (25.5% of the total). About 64% of the total assemblage is well preserved and displays features comparable to those seen in fresh modern specimens. Large depressed circles (Fig. 2F) are noticeable in the center of 639 specimens (27% of the total starch assemblage). Enlarged fissures (Fig. 2G) total 190 (8%). There are 37 instances (~1.5% of the total) in which clumps fused, with gelatinized grains that show flat reliefs, expanded size, and a loss of birefringence. Because the starch-containing artifacts come from dark chambers of the cave, these biogenic polymers cannot derive from in situ, naturally growing plants. Starch preservation over such a long period of time might be due to the formation of a molecular film over the stone surface through adsorption, which, once complete, retards or abolishes the utilization of the adsorbate by microbes (*3*).

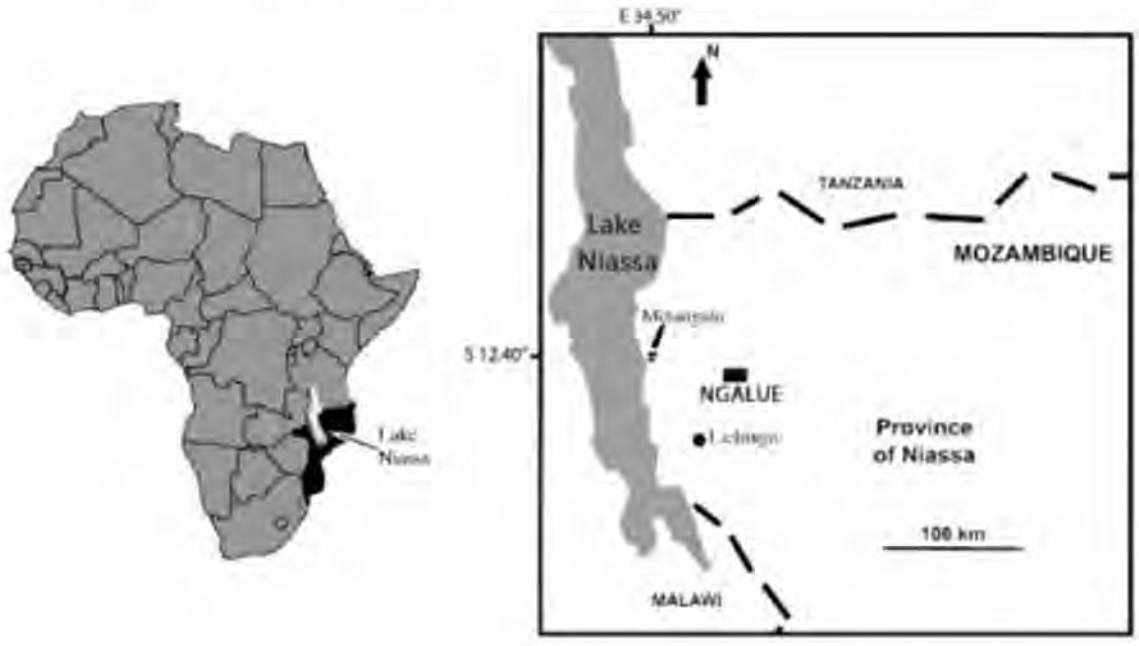

Fig. 1. Study area and site location.

Table 1. Starch and stone tools.

Starch on lithics	Lithics (n)	Granules (n)	Mean (range)
Scrapers (n = 25)			
Side scraper	1	6	6
Core scraper	17	1088	64 (0–654)
Convergent scraper	6	103	17 (1–44)
Denticulate scraper	1	1	1
Subtotal		1198	
Average mean		22	
Cores, core tools (n = 18)			
Discoidal core	6	46	7 (0–23)
Micro discoidal core	4	12	3 (0–12)
Blade core	1	2	2
Core (other)	3	211	105 (17–211)
Core axe	1	71	71
Polished grinder	2	177	88 (77–100)
Anvil	1	83	83
Subtotal		602	
Average mean		51	
Points (n = 10)			
Levallois point	1	38	38
Shouldered point	2	24	12 (3–21)
Point, classic	6	91	26 (4–91)
Point, thick base	1	1	1
Subtotal		154	
Average mean		20	
Flakes, blades (n = 5)			
Levallois flake, retouched	2	365	182 (7–358)
Flake	2	2	1
Blade	1	2	2
Subtotal		369	
Average mean		61	
Other tools (n = 13)			
Small cleaver	1	1	1
Drill	3	13	4 (0–7)
Small pebble tool	4	32	8 (0–29)
Microlith	2	0	0
Geometric	2	0	0
Subtotal		46	
Average mean		2	

Of the 2369 grains retrieved, 89% (n = 2112) are *Sorghum spp.* (Table 1). *Sorghum* shows an extremely variable complex of cultivated, wild, and weedy taxa that defy formal taxonomy (*4*, *5*). All domesticated sorghums derive from *Sorghum bicolor* subsp. *arundinaceum* (5), and they group in three complexes, one of which is restricted to Ethiopia. Modern sorghum grows naturally in the Zambezian Miombos of the study region, including *Sorghum bicolor* subsp. *bicolor*, race Kafir; and Sorghum *bicolor* subsp. *arundinaceum*, the common wild sorghum. In general, *Sorghum bicolor* makes starches with several shapes, roughly polygonal and rounded, between 5 and 25 μm across (the average for modern sorghum granules is 15 μm) (*6*). The sorghum grains from the prehistoric assemblage have a mean maximum length of 16.6 ± 3.6 μm (n = 264; minimum, 6.5 μm; maximum, 25.3 μm), which is very close to the modern value. The ancient starch grains display morphologies like those seen in modern *Sorghum bicolor* subsp. *bicolor* (*7*–*9*) and in the reference materials from *Sorghum bicolor* subsp. *arundinaceum*. On the basis of granule shapes (*7*–*9*), another subset of 427 prehistoric, putative sorghum granules is made up of 43% corneous endosperm (orthogonal subspheres) (Fig. 2, A and B), 39%

floury endosperm (rounded grains) (Fig. 2C), and 18% from undetermined provenances within the grain (tabular shapes) (Fig. 2D). Six grains have vase shapes (Fig. 2E) like those of sorghum and closely related taxa (*9*).

The starch on Mozambican lithics shows that woody plants were also exploited during the Middle Stone Age. Lenticular granules with ellipsoid-to-orbicular bodies, lamellae, tenuous centric slits, depressions, pocking, and an incision along the equatorial plane (Fig. 2H) (n = 83) represent 3.5% of all recovered starches. The mean size is 23.5 ± 6 μm (range, 8 to 36.6 μm). This morphology has been discovered in the seeds, legumes, nuts, and mesocarp from several species in the Fabaceae, Malvaceae, and Apocynaceae (*3*). Another group of starches includes a pear-shaped body with one tapered end, ellipsoid lamellae, an eccentric cross, sometimes a cuneiform slit, and creases (n = 68; Fig. 2L). It represents 3% of the total assemblage. This sample shows a wide range in size: 17 to 67 μm (mean, 37.6 ± 10.8 μm). The closest match is in the starches from the pith of the Arecaceae; specifically, the trunk of the African wine palm (*Hyphaene petersiana*). An additional starch morphotype is pointed (n = 11, Fig. 2J). It has a hyperellipsoidal shape (it resembles a rod in three dimensions) with a highly eccentric cross and bent arms. The appearance of this type is restricted to three tools: a grinder, a core axe, and a Levallois flake. Its mean maximum length is 40 μm (range, 21 to 68 μm). It matches starches from the Musaceae, namely, those from the mesocarp and corm tissues of the African false banana (*Ensete ventricosum*). Lastly, I found 12 clusters of compound or fused small granules (~2 μm) on a grinder/core axe. The closest equivalent is found in two members of the Hypoxidaceae: *Hypoxis hemerocallidea* (the African potato) and *Hypoxis iridifolia*.

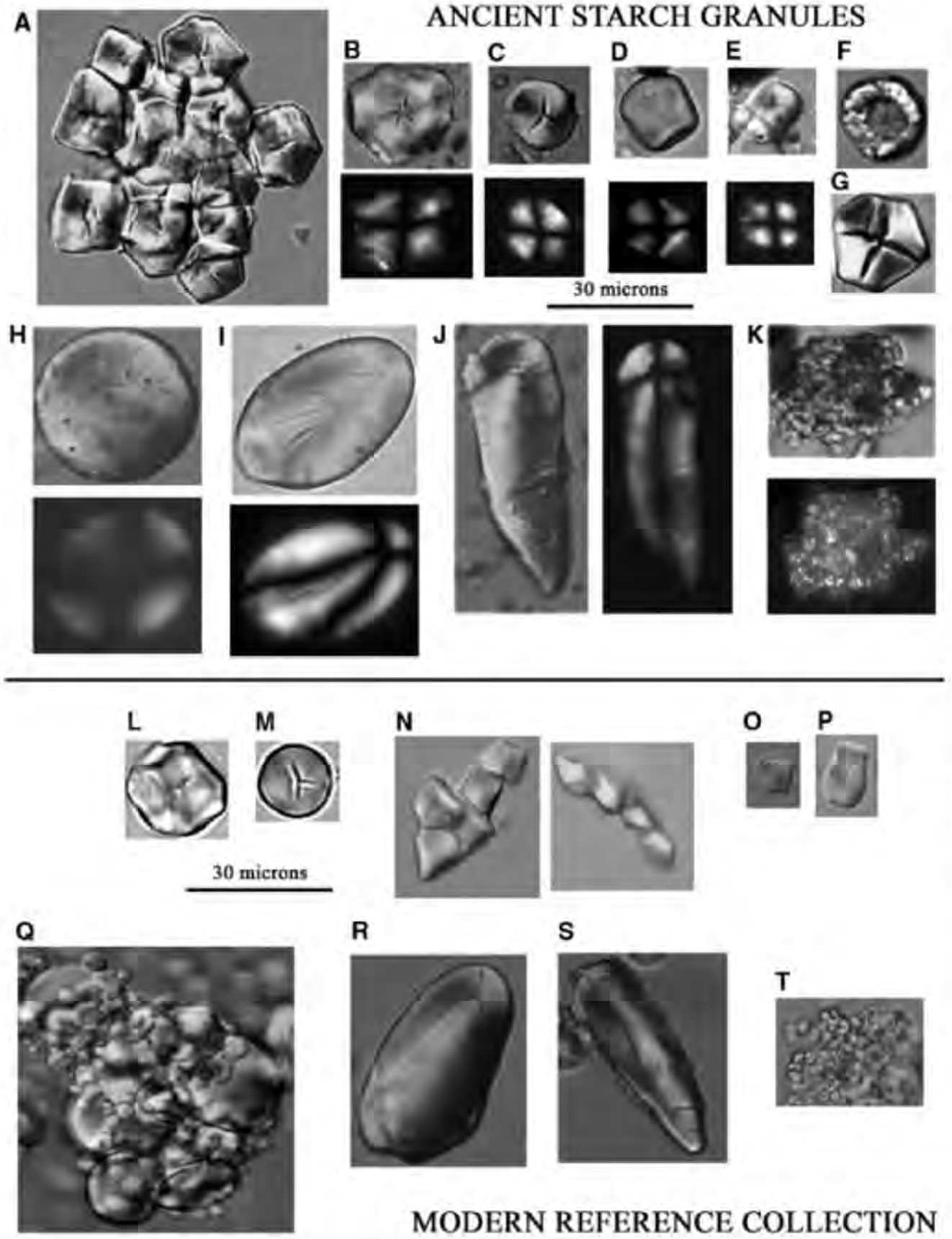

Fig. 2. Selected archaeological granules from *Sorghum* spp. include the following: (**A**) from stone tool no. 23, (**B**) from no. 18, (**C**) from no. 20, (**D**) from no. 2, (**E**) from no. 2, (**F**) from no. 56, and (**G**) from no. 2; (**H**) from no. 2, probably a seed type from woody taxa; (**I**) from no. 66, probably from the trunk of the African wine palm *Hyphaene* spp.; (**J**) from no. 18; probable source, the African false banana (*Ensete ventricosum*); and (**K**) from no. 19; likely source, the African "potato" (*Hypoxis* spp.). Selected modern reference material is from the grain endosperm of *Sorghum bicolor* subsp. *arundinaceum* (Poaceae) (**L** to **P**). Tabular shapes are shown in (N) (abaxial and side views, respectively). Vase shapes appear in (O) to (P). Lenticular starches from (**Q**) are from the legume of *Delonix* spp. (Fabaceae). Starch granules from the trunk of *Hyphaene petersiana* (Arecaeae) are exemplified in (**R**). The starch from the corm of *Ensete ventricosum* (Musaceae) is shown in (**S**), and the starch from the corm of *Hypoxis hemerocallidea* (Hypoxidaceae) is in (**T**).

Fifteen stone tools yielded large numbers of altered starch granules. The most frequent damage pattern is documented on stone tool no. 61, which presents 449 instances of flattened granules with an enlarged centric hole and a bulge around the edges (Fig. 2F). Marked transversal fissures appear in at least 70 additional granules from the same stone tool (Fig. 2G). The alterations are associated with other modifications such as loss of birefringence, breakage, surface roughening, and radial fissuring. Several possibilities may account for the observed modifications, including aging and bacterial attack, culinary-induced modifications to the native starch grain (for example, from boiling), and/or hydrolysis during fermentation and/or grinding (*10*, *11*). Establishing the mode of use of starch resources through granule alteration patterns, however, requires a different type of research and additional proof beyond the altered granules alone.

The Mozambican data show that Middle Stone Age groups routinely brought starchy plants

Fig. 3. Examples of high-starch–bearing grinding and pounding implements from Ngalue cave.

to their cave sites and that starch granules got attached to and preserved on stone tools. I cannot prove that starch from all stone tools represents direct tool function (*12*, *13*). Core tools and scrapers were exposed to starches more often than other tool types. Three-quarters of the starch assemblage comes from chipped stone, not ground or polished tools. African Middle Stone Age lithic repertoires do not yield large quantities of dedicated grinders that would demonstrate the processing of seeds. These early grinders are simply modified cobbles and core tools (Fig. 3) (*14*), with a suspected use that conforms to the technological action known as "diffuse resting percussion" and "pounding" (*15*), which allow the grinding of plant materials. It is not clear why the tools should be mostly coated with grass starches and not so much with other types of starch. It is possible that high-starch–bearing grass refuse built up considerably in the cave's main chamber at times of human occupation, thus coating both tools that were used in the processing of grass seeds and others that were not. These data imply that early *Homo sapiens* from southern Africa consumed not just underground plant staples (*16*) but above-ground resources too.

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Supporting Online Material

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Universality in Three- and Four-Body Bound States of Ultracold Atoms

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Under certain circumstances, three or more interacting particles may form bound states. Although the general few-body problem is not analytically solvable, the so-called Efimov trimers appear for a system of three particles with resonant two-body interactions. The binding energies of these trimers are predicted to be universally connected to each other, independent of the microscopic details of the interaction. By exploiting a Feshbach resonance to widely tune the interactions between trapped ultracold lithium atoms, we find evidence for two universally connected Efimov trimers and their associated four-body bound states. A total of 11 precisely determined three- and four-body features are found in the inelastic-loss spectrum. Their relative locations on either side of the resonance agree well with universal theory, whereas a systematic deviation from universality is found when comparing features across the resonance.

One of the most notable few-body phenomena is the universally connected series of three-body bounds states first predicted by Efimov (*1*) in 1970. Efimov showed that three particles can bind in the presence of resonant two-body interactions, even in circumstances where any two of the particles are unable to bind. When the two-body scattering length a is much larger than the range of the interaction potential r_0, the three-body physics becomes independent of the details of the short-range interaction. Surprisingly, if one three-body bound state exists, then another can be found by increasing a by a universal scaling factor, and so on, resulting in an infinite number of trimer states (*2*). Universality is expected to persist with the addition of a fourth particle (*3*–*7*), with two four-body states associated with each trimer (*5*, *7*). Intimately tied to the three-body state, these tetramers do not require any additional parameters to describe their properties.

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Ultracold atoms are ideal systems for exploring these weakly bound few-body states because of their inherent sensitivity to low-energy phenomena, as well as the ability afforded by Feshbach resonances to continuously tune the interatomic interactions. Pioneering experiments with trapped, ultracold atoms have obtained signatures of individual Efimov states (*8*–*12*)—as well as two successive Efimov states (*13*, *14*)—via their effect on inelastic collisions that lead to trap loss. Evidence of tetramer states associated with the trimers has also been found (*13*, *15*). Although the locations of successive features are consistent with the predicted universal scaling, systematic deviations as large as 60% were observed and attributed to nonuniversal short-range physics (*13*). In the work presented here, we use a Feshbach resonance in ^{7}Li for which a/r_0 can be tuned over a range spanning three decades (*16*). This enables the observation of multiple features that are compared to universal theory.

We confine ^{7}Li in the $|F = 1, m_F = 1\rangle$ (where F is the total spin quantum number and m_F is its projection) hyperfine state in an elongated, cylindrically symmetric, hybrid magnetic—plus—optical dipole trap, as described previously (*16*). A set of Helmholtz coils provides an axially oriented magnetic bias field that we used to tune the two-body scattering length a via a Feshbach resonance located near 737 G (*17*). For $a > 0$, efficient evaporative cooling is achieved by setting the bias field to 717 G, where $a \sim 200a_0$ (a_0 is the Bohr radius), and reducing the optical-trap intensity. Depending on the final trap depth, we create either an ultracold thermal gas just above the condensation temperature T_C or a Bose-Einstein condensate (BEC) with >90% condensate fraction. For investigations with $a < 0$, we first set the field to 762 G where $a \sim -200a_0$ and proceed with optical-trap evaporation, which is stopped at a temperature T slightly above T_C. In both cases the field is then adiabatically ramped to a final value and held for a variable hold time. The fraction of atoms remaining at each time is measured via in situ polarization phase-contrast imaging (*18*) for clouds where the density is high, or absorption imaging in the case of lower densities.

Analyzing the time evolution of the number of atoms in the trap determines the three-body loss coefficient L_3 (*8*, *13*, *19*), as well as the four-body loss coefficient L_4 (*15*). Recombination into a dimer is a three-body process because a third atom is needed to conserve both momentum and energy. For $a > 0$, the dimer can be weakly bound with binding energy $\varepsilon = \hbar^2/(ma^2)$ (where m is the atomic mass and $\hbar$ is Planck's constant h divided by 2π), whereas for $a < 0$ there are only deeply bound molecular dimers. The recombination energy released in the collision is sufficient to eject all three atoms from the trap for $a < 0$, as well as for $a > 0$ when $\varepsilon \gtrsim U$ (where U is the trap depth). In the case of the BEC data, this latter condition holds for $a \lesssim 5000a_0$. Nonetheless, we assume that all three atoms are lost for any recombination event because, even for a larger than $5000a_0$, we observe rapid three-body

loss. We ascribe this observation to a high probability for dimers to undergo vibrational relaxation collisions that result in kinetic energies much greater than U. Four-body processes proceed in a similar fashion (*6*, *15*).

The equation describing the dynamics of three- and four-body loss is

$$\frac{1}{N}\frac{dN}{dt} = -\frac{g^{(3)}}{3!}L_3\langle n^2\rangle - \frac{g^{(4)}}{4!}L_4\langle n^3\rangle \quad (1)$$

where N is the total number of atoms in the trap at time t, and the brackets denote averages over the density distribution n (*17*). For a thermal gas, the spatial correlation coefficients $g^{(3)}$ and $g^{(4)}$ are, respectively, 3! and 4!, whereas for a BEC, both are set to 1 (*20*, *21*). We have verified that heating from recombination is small for our short observation times and therefore omit this effect in our analysis (*15*, *19*). By fitting the time evolution of the number of atoms to the solution of Eq. 1, we extract L_3 and L_4 as a function of a. Figure S1 shows the loss of atoms as a function of time in regimes where either L_3 or L_4 dominates (*17*). Four-body loss is readily distinguished from three-body loss by the shape of the loss curve.

Figure 1 shows the extracted values of L_3 across the Feshbach resonance, exhibiting the expected a^4 scaling (*22*, *23*), but with several dips and peaks punctuating this trend. Two prominent peaks, labeled a_1^- and a_2^- in Fig. 1A, dominate the landscape for $a < 0$. We attribute

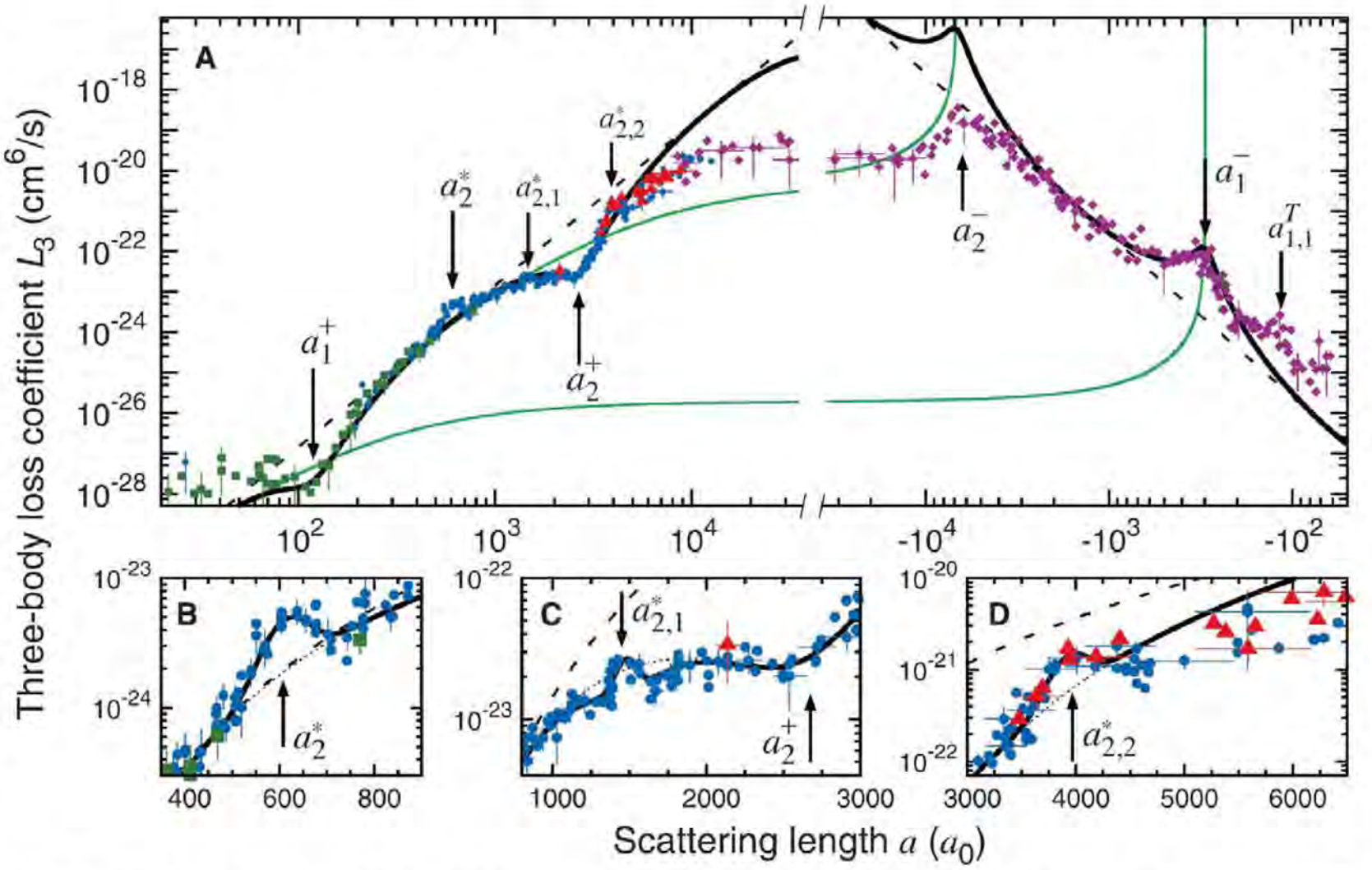

Fig. 1. (**A**) L_3 as a function of a. Data shown with purple diamonds correspond to a thermal gas with $N \sim 10^6$, $T \sim 1$ to 3 μK (*31*), and $U \sim 6$ μK and were taken with radial and axial trapping frequencies $\omega_r = (2\pi)$ 820 Hz and $\omega_z = (2\pi)$ 7.3 Hz, respectively. The remaining data correspond to a BEC with $N \sim 4 \times 10^5$, $T < 0.5\ T_C$, $U \sim 0.5$ μK, and $\omega_r = (2\pi)$ 236 Hz. We adjust ω_z (*17*) to enhance or reduce three-body loss, where $\omega_z = (2\pi)$ 1.6 Hz (red triangles), $\omega_z = (2\pi)$ 4.6 Hz (blue circles), and $\omega_z = (2\pi)$ 16 Hz (green squares). The black dashed lines show an a^4 scaling, and the thick black solid lines are fits to an analytic theory (*2*, *17*). The thin green lines show the square of the energies (in arbitrary units) of the first and second Efimov states, as predicted from the universal theory (*2*), where we have fixed the location of the first Efimov state to overlap with a_1^-, and the atom-dimer continuum is coincident with the dashed line for $a > 0$. Several representative error bars indicating the SE from the fit are shown (*17*). (**B** to **D**) Detail around the loss features associated with the atom-dimer and two possible dimer-dimer resonances. The black dotted lines are fits to eq. S4, whereas the black solid lines include additional superimposed Gaussian fits to account for the features not described by eq. S4.

Table 1. Locations (in a_0) of three- and four-body loss features and inelasticity parameters (dimensionless) (*17*). The features $a_{2,1}^*$ and $a_{2,2}^*$ are tentatively assigned. The first number in parentheses characterizes the range over which χ^2 of the fit to theory increases by one while simultaneously adjusting the other parameters in the fit. The second number characterizes the systematic uncertainties in the determination of a (*17*).

$a > 0$	$a < 0$
$a_1^+ = 119(11)(0)$	$a_1^- = -298(10)(1)$
$a_2^+ = 2676(67)(128)$	$a_2^- = -6301(264)(740)$
$a_2^* = 608(11)(7)$	$a_{1,1}^T \sim -120(20)(0)$
$[a_{2,1}^* \approx 1470(15)(38)]$	$a_{1,2}^T \approx -295(35)(1)$
$[a_{2,2}^* \approx 3910(60)(278)]$	$a_{2,1}^T \approx -2950(200)(150)$
$\eta_1^+ = 0.079(32)(20)$	$a_{2,2}^T \approx -6150(800)(700)$
$\eta_2^+ = 0.039(4)(10)$	$\eta^- = 0.13(1)(3)$

Table 2. Relative locations of loss features, those predicted by theory, and the percent difference Δ = (data/theory − 1). The uncertainties are those propagated from Table 1.

	Ratio	Data	Theory	Δ(%)
$a > 0$	a_2^+/a_1^+	22.5(22)(11)	22.7*	−1(9)(5)
	a_2^+/a_2^*	4.40(14)(16)	4.46*	−1(3)(4)
	$a_{2,1}^*/a_2^*$	≈2.42(5)(4)	2.37‡	+2(2)(2)
	$a_{2,2}^*/a_2^*$	≈6.4(2)(4)	6.6‡	−3(2)(6)
$a < 0$	a_2^-/a_1^-	21.1(11)(24)	22.7*	−7(5)(11)
	$a_{1,1}^T/a_1^-$	~0.40(7)(0)	0.43†	−6(16)(0)
	$a_{1,2}^T/a_1^-$	≈0.99(12)(0)	0.90†	+10(14)(0)
	$a_{2,1}^T/a_2^-$	≈0.47(4)(4)	0.43†	+9(9)(9)
	$a_{2,2}^T/a_2^-$	≈0.98(13)(1)	0.90†	+8(14)(1)
$a \to \pm\infty$	$\lvert a_1^-\rvert/a_1^+$	2.5(2)(0)	4.9*	−49(5)(0)
	$\lvert a_2^-\rvert/a_2^+$	2.4(1)(4)	4.9*	−52(2)(9)
	$\lvert a_1^-\rvert/a_2^*$	0.49(2)(1)	0.97*	−49(2)(1)
	$\lvert a_2^-\rvert/a_2^*$	10.4(5)(14)	22.0*	−53(2)(6)

*See (*2*). †See (*7*). ‡See (*28*).

these peaks to the crossings of the energies of the first two trimer states with the free-atom threshold, thus providing additional pathways into deeply bound molecular states (*23*). For $a > 0$, the dominant features are dips, indicated in Fig. 1A as a_1^+ and a_2^+, corresponding to recombination minima. These minima are associated with the merging of the same two trimer states into the atom-dimer continuum and have been attributed to destructive interference between two different decay pathways into weakly bound dimers (*22*, *23*). We fit the data to $L_3(a) = 3C(a)\hbar a^4/m$, where $C(a)$ is a logarithmically periodic function characterizing effects from the Efimov states (*17*). The analytic expression for $C(a)$ contains the location of one universal trimer resonance $a^- < 0$ or recombination minimum $a^+ > 0$ and an inelasticity parameter η related to the lifetime of the Efimov state (*2*). The observed features are fit individually to extract these parameters (Table 1). The universal theory describing Efimov physics (*2*) predicts a logarithmic spacing in the two-body scattering length between trimer states of $e^{\pi/s_0} \approx 22.7$, where $s_0 = 1.00624$ is a universal parameter (*1*). Table 2 shows that the ratios a_2^+/a_1^+ and a_2^-/a_1^- agree well with the universal theory.

A local maximum in L_3, indicated as a_2^* and shown in detail in Fig. 1B, can be discerned between the two recombination minima a_1^+ and a_2^+. We associate this feature with an atom-dimer resonance, given its location with respect to the nearby minima. A simple model (*13*) has been proposed to explain the enhanced losses present at the atom-dimer resonance. This model describes an avalanche process whereby a single dimer traveling through a collisionally thick gas shares its kinetic energy with multiple atoms, thereby increasing from three the effective number of atoms lost for each dimer formed (*24*).

For $a < 0$, L_3 achieves its maximum value of $\sim 10^{-19}$ cm^6/s at a_2^-. This value is reasonably consistent with the expected unitarity limit (*19*, *25*). At even larger values of $|a|$, L_3 saturates to a value below the unitarity limit, a behavior previously seen in experiments (*8*) and numerical calculations (*25*, *26*).

The four-body loss coefficient (L_4) for $a < 0$ was also extracted from the data, and the results are presented in Fig. 2. Three resonant peaks in L_4 are observed, which we associate with the crossings of tetramer states with the free-atom continuum (*3*–*7*, *13*, *15*, *27*). Two universal tetramers are predicted to accompany each Efimov trimer (*5*, *7*). The black solid line in Fig. 2 is calculated using only the observed three-body locations and widths, in addition to an overall scaling, without any other free parameters (*17*). The agreement between this curve and the data lead us to assign the peaks to the second tetramer of the first Efimov trimer, $a_{1,2}^T$, and both tetramers of the second Efimov trimer, $a_{2,1}^T$ and $a_{2,2}^T$ (*15*). Although we do not have the resolution to detect an enhancement in L_4 at the expected location of the first tetramer $a_{1,1}^T$, an enhancement of L_3 is observed at the expected location (Fig. 1A), which we tentatively identify with $a_{1,1}^T$ (*7*, *13*). The existence of two tetramer states tied to a single trimer state has also been verified in ^{133}Cs (*15*) and ^{39}K (*13*).

Two additional peaks in L_3 are observed on the $a > 0$ side of the resonance (Fig. 1, C and D). Features at these relative positions have not been previously observed or predicted, although they occur very close to where the two tetramer states associated with the second trimer are expected to merge with the dimer-dimer continuum (*28*). We have no explanation of how a dimer-dimer resonance would affect the inelastic-loss rate, as we expect the dimer fraction to be small and, consequently, the probability of dimer-dimer collisions to be negligible. One possibility is that they arise because of an interference effect, similar to that occurring in the three-body process at a_1^+ and a_2^+. Presently, we tentatively associate these features with dimer-dimer resonances located at $a_{2,1}^*$ and $a_{2,2}^*$.

In Table 2, we present the relative spacings of observed loss features along with those predicted by the universal theory. Universal scaling is expected when $|a| \gg r_0$, where r_0 is the van der Waals radius ($33a_0$ for Li) (*29*). Another requirement for universality is that $|a| \gg |R_e|$, where R_e is the effective range (*14*). Figure S4 shows that R_e is relatively small over the relevant field range and is $\sim -10a_0$ on resonance (*17*). For comparison, in the $|1, 0\rangle$ state of ^{7}Li, $R_e \sim -30a_0$ at the resonance near 894 G (*14*). Both conditions for universality are well-satisfied for the second Efimov state, but the requirement that $|a| \gg r_0$ is only marginally satisfied for the first. Nonetheless, we find good agreement with the universal scaling relations between features on each side of the Feshbach resonance separately.

The features across a Feshbach resonance are also thought to be universally connected (*2*, *26*). However, when we compare features across the Feshbach resonance, we find a systematic discrepancy with theory of a factor of 2 (Table 2). This discrepancy can be expressed as a difference in the three-body short-range phase between the two sides of the Feshbach resonance $\Delta\Phi = s_0 \ln(|a^-|/a^+)$ (*22*, *26*). The locations of the features reported here result in phase differences of 0.92(10)(0) and 0.86(4)(17) (the uncertainties are defined in Table 1) for the first and second trimer, respectively, whereas the universal prediction is 1.61(3) (*2*). Finite temperature causes the trimer resonances to broaden and shift toward smaller $|a|$ (*8*, *25*, *26*). This would decrease the values of $\Delta\Phi$, because we extract L_3 from a thermal cloud at a^- and a much colder BEC at a^+. Measurements of ^{39}K also show a discrepancy with theory across the resonance, but with $\Delta\Phi = 1.91(7)$ (*13*). On the other hand, measurements of the first trimer resonance and second trimer recombination minimum in the $|1, 0\rangle$ state of ^{7}Li result in $\Delta\Phi = 1.7(2)$, in good agreement with universal theory, assuming the universal scaling of 22.7 between trimer states (*14*). These variations in $\Delta\Phi$ may indicate the need for additional physics to be included in the universal model (*26*, *30*).

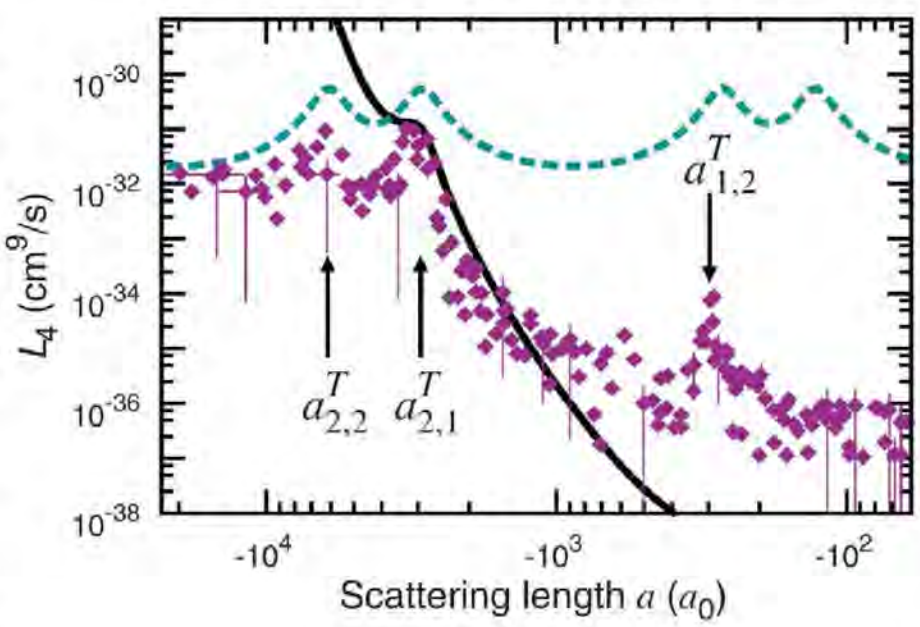

Fig. 2. L_4 extracted from a thermal gas. The black solid curve is motivated by theory (*17*, *27*), and the blue dashed curve is the solid curve divided by a^7 (*6*). The uncertainty in L_4 from the fit is a factor of 2, whereas the systematic uncertainty is a factor of 3 due to uncertainties in ω_r, ω_z, N, and T. For $|a| > 2 \times 10^4 a_0$, differentiation between three- and four-body losses becomes unreliable because of the very fast decay rates. Data with $L_4 < 10^{-36}$ cm^9/s are consistent with no four-body loss.

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31. In ramping from $-200a_0$ to $a < -3000a_0$, we observe an increase in the axial size of the thermal cloud that is consistent with a temperature increase of the cloud to ~3 μK. During the trap-loss measurements, we observe negligible change in the Gaussian width of the thermal cloud (*17*).
32. We thank E. Olson for his contributions to this project and acknowledge useful discussions with E. Braaten, J. P. D'Incao, C. H. Greene, N. P. Mehta, and H. T. C. Stoof. Support for this work was provided by the NSF, Office of Naval Research, the Keck Foundation, and the Welch Foundation (grant C-1133).

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Experimental Observations of Stress-Driven Grain Boundary Migration

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In crystalline materials, plastic deformation occurs by the motion of dislocations, and the regions between individual crystallites, called grain boundaries, act as obstacles to dislocation motion. Grain boundaries are widely envisaged to be mechanically static structures, but this report outlines an experimental investigation of stress-driven grain boundary migration manifested as grain growth in nanocrystalline aluminum thin films. Specimens fabricated with specially designed stress and strain concentrators are used to uncover the relative importance of these parameters on grain growth. In contrast to traditional descriptions of grain boundaries as stationary obstacles to dislocation-based plasticity, the results of this study indicate that shear stresses drive grain boundaries to move in a manner consistent with recent molecular dynamics simulations and theoretical predictions of coupled grain boundary migration.

The strength and ductility of materials are inherently related to processes that govern the way that atoms move past one another, and, in crystalline metals, plastic deformation is most often associated with the way that dislocations (linear crystalline defects) move through individual crystals called grains. The mechanical behavior of metals and alloys can be tailored by introducing microstructural obstacles to dislocation motion; solid solution strengthening, precipitation hardening, and grain boundary strengthening are all examples of this. The latter is related to the fact that dislocation glide in polycrystalline metals is limited by the presence of grain boundaries and the misorientation between grains that they embody. The general realization that smaller grain-sized materials (possessing a higher density of grain boundaries) are stronger has lead to the often-cited Hall-Petch relation, which states that strength scales with the reciprocal square root of grain size (*1*, *2*) and assumes that grain boundaries act as obstacles to plastic deformation within the material.

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Materials scientists traditionally describe the detailed geometric structure of grain boundaries through a coincident site lattice (CSL), which promotes the view of grain boundaries as mechanically static, immovable structures. However, recent studies involving nanocrystalline materials have introduced convincing evidence to suggest that grain boundaries are not static; mechanically induced room temperature grain growth has been associated with indentation (*3*–*5*), compression (*6*, *7*), and tensile loading (*8*–*11*). These observations cannot be described by classical models of grain growth (*8*) and were originally characterized as strain-driven grain boundary migration (*4*). Subsequent experiments quantifying grain growth in terms of temperature (*5*), strain rate (*10*), proximity to crack tips (*12*), and testing mode (*7*) suggested that grain boundary migration in nanocrystalline metals may be driven more by stress than by plastic strain. The experiments outlined below demonstrate that the room-temperature grain growth observed in nanocrystalline metals is associated with shear stress-driven grain boundary migration, thereby confirming recent theories of coupled grain boundary migration (*13*, *14*) and confirming that grain boundaries are not static structures as traditionally assumed.

It is widely acknowledged that shear stresses drive dislocation motion. The motion of low-angle grain boundaries, which consist of dislocation arrays, under shear stress can be described by the collective movement of the individual dislocations in these boundaries (*15*, *16*). By contrast, the concept of shear stress moving a high-angle grain boundary is relatively foreign to the materials science community, with experimental observations of such a mechanism being elusive. Cahn and co-workers (*13*) have recently published a unified theory of coupled grain boundary motion based on the supposition that the normal motion of a grain boundary couples to the tangential displacement (shear) of adjacent grains. Molecular dynamics simulations (*14*, *17*) and bicrystal experiments (*18*–*20*) involving the migration of specific high-angle tilt boundaries have been shown to be consistent with Cahn's theory of coupled boundary migration. Recent molecular dynamics simulations (*21*) suggest that a fraction of general grain boundaries do exhibit anomalously high mobility when operating in a shear coupled mode, but experimental extensions to a more general population of boundaries, where grain boundaries are composed of a combination of twist and tilt character and bounded by grain boundary junctions, have proven much harder to realize. Moreover, the need for measurable grain boundary mobility requires that the bicrystal experiments be done at elevated temperature, making the separation of mechanical and thermal effects problematic. The occurrence of room-temperature grain growth in nanocrystalline metals offers the opportunity to impose much higher stresses on a much wider range of boundaries without the superposition of elevated temperature. This study was specifically designed to test the hypothesis that shear stresses can directly cause high-angle grain boundaries to move. The experiments described here allowed the investigation of the influence of normal and shear stresses and strains on the motion of a wide population of grain boundaries as encountered in most polycrystalline materials, without the need to characterize adjacent nanocrystalline grains and boundaries with high fidelity.

In order to elucidate the effect of stress and strain on mechanically induced grain growth, we have borrowed a page from the fracture mechanics community, where geometric concentrators have been used to discriminate between stress-controlled brittle fracture and strain-controlled ductile fracture (*22*, *23*). We present experiments on freestanding nanocrystalline Al thin films, where spatial variations in the stress and strain states were deliberately introduced by using special sample geometries. A major benefit of our approach lies in

the ability to study a statistical ensemble of grains and their evolution because the individual grains are much smaller than the gradients of the stress and strain fields. This allowed us to collect sufficient data from transmission electron microscopy (TEM) to statistically characterize how microstructure evolves under a specific deformation field. Combining systematic and quantitative microstructural analysis with continuum descriptions of stress and strain gradients allowed us to distinguish between the effects of stress and strain on grain growth.

Microtensile free-standing thin film specimens with hole patterns (50-μm radius) in the gage section (700 μm by 4 mm) were fabricated as shown in Fig. 1, A and B, deformed, and examined by using post-mortem TEM. All films were deposited to thicknesses of 150 to 220 nm by using pulsed electron beam evaporation, which limited the growth of through-thickness grains and yielded average grain sizes of 60 to 90 nm with large numbers of high-angle boundaries and no preferred crystallographic texture (Fig. 1, C and D). Observations of room-temperature grain growth in undeformed nanocrystalline materials have been reported [see, for example, (*24*)], but the films used in the current study were stable at room temperature and showed no evidence of spontaneous thermal grain growth. Interior holes were added to traditional tensile geometries with photolithography and used to exploit the fact that, with local yielding, the maximum strain occurs at the hole edge while the maximum stress is offset from the edge (*22*, *23*, *25*). In this way, a specimen with two holes situated horizontally (referred to as the horizontal-hole geometry) (Fig. 1A) was used to study and contrast the effects of stress and strain on grain growth. The influence of stress state was studied by patterning two holes collinearly at a 45° angle from the tensile axis (referred to as the angled-hole geometry) (Fig. 1B); the overlapping stress fields resulted in well-separated regions of increased shear and normal stresses. For both types of specimens, the gradients in stress and strain exist on a much larger scale (tens of micrometers) than the length scale associated with the material microstructure (tens of nanometers), meaning a large number of grains felt the altered stress or strain state. Although plastic strain can introduce local heterogeneities on the order of the microstructure, statistical averaging of grain growth over areas that contain hundreds of grains is expected to mitigate the influence of these local perturbations. Spatial variations in grain growth were quantified by using bright field TEM images to obtain grain size distributions at different specimen positions. Over 100 grain sizes were measured for each data set, and Welch's *t* test was used to ensure that the observed measurements of grain growth were statistically significant. Trends in grain growth for multiple specimens and specimen geometries were then reconciled with the results of finite element analysis (FEA), which predicted the full-field stress and strain distributions in the various specimens and included the effects of stress-induced wrinkling in freestanding thin films (figs. S1 and S2). Details for the experimental tensile setup and FEA can be found in (*26*).

Horizontal-hole specimens were first used to measure the relative importance of stress and strain in driving mechanically induced grain growth. Remote axial displacements of 25 to 30 μm were applied to the specimens, and the corresponding stress and strain fields were calculated by using a finite element mesh of the specimen, plasticity laws determined from uniaxial tensile experiments, and contributions from mechanical wrinkling (displacements out of the plane of the specimen). The stress and strain contours predicted by the FEA are shown in Fig. 2. The maximum normal and shear stresses both rise gradually with increasing distance from the hole perimeter, reach a local maximum at about half of the hole radius (~25 μm), and fall off beyond this point. It should be noted that the heterogeneity and asymmetry in the stress and strain fields arise because of wrinkling-induced relaxations and local plasticity. By contrast, the maximum normal and distortional plastic strains were found to be highest at the edge of the hole and to fall off rapidly away from that edge. The grain growth was characterized in two well-defined regions: region 1, where the strains are greatest, and region 2, where the stresses are highest. The measured grain size distributions are summarized in Fig. 2, where cumulative distribution plots (Fig. 2F) illustrate the fact that grain growth occurred in both regions but was greatest in region 2. This finding points to the role of stress in promoting grain growth. Additional statistical parameters for characterizing the microstructure of each region, along with average stress and strain values from FEA, can be found in table S1.

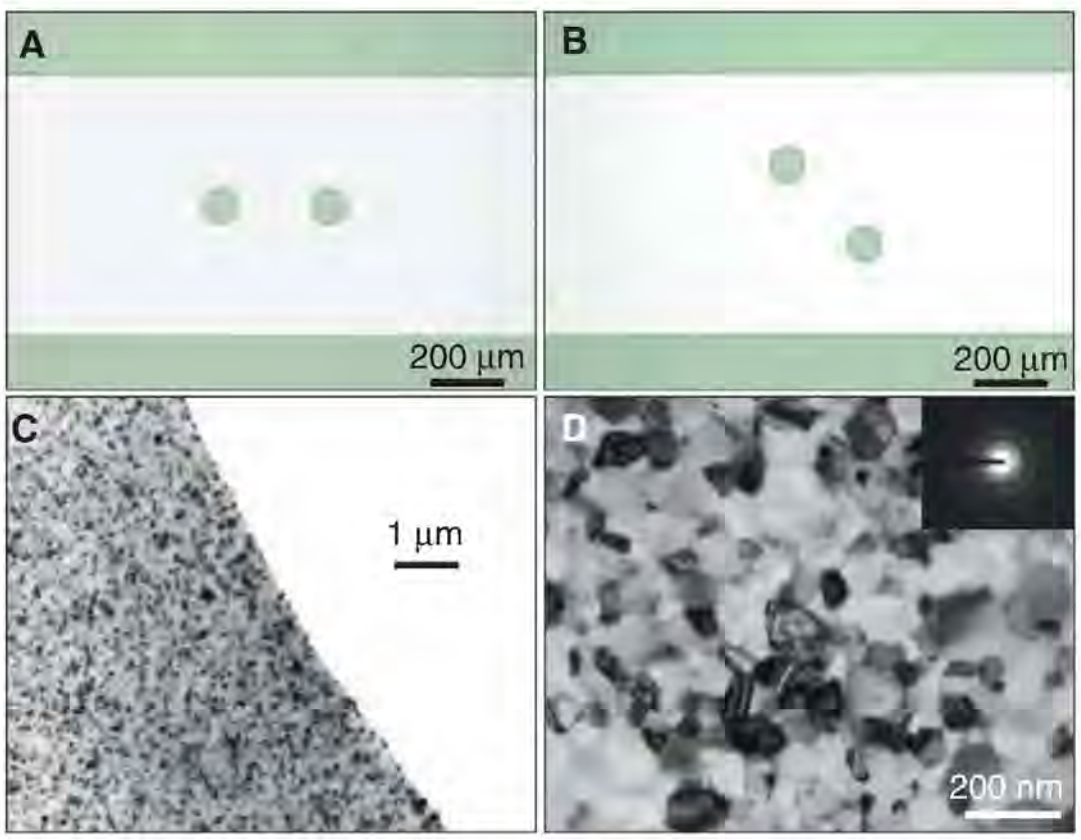
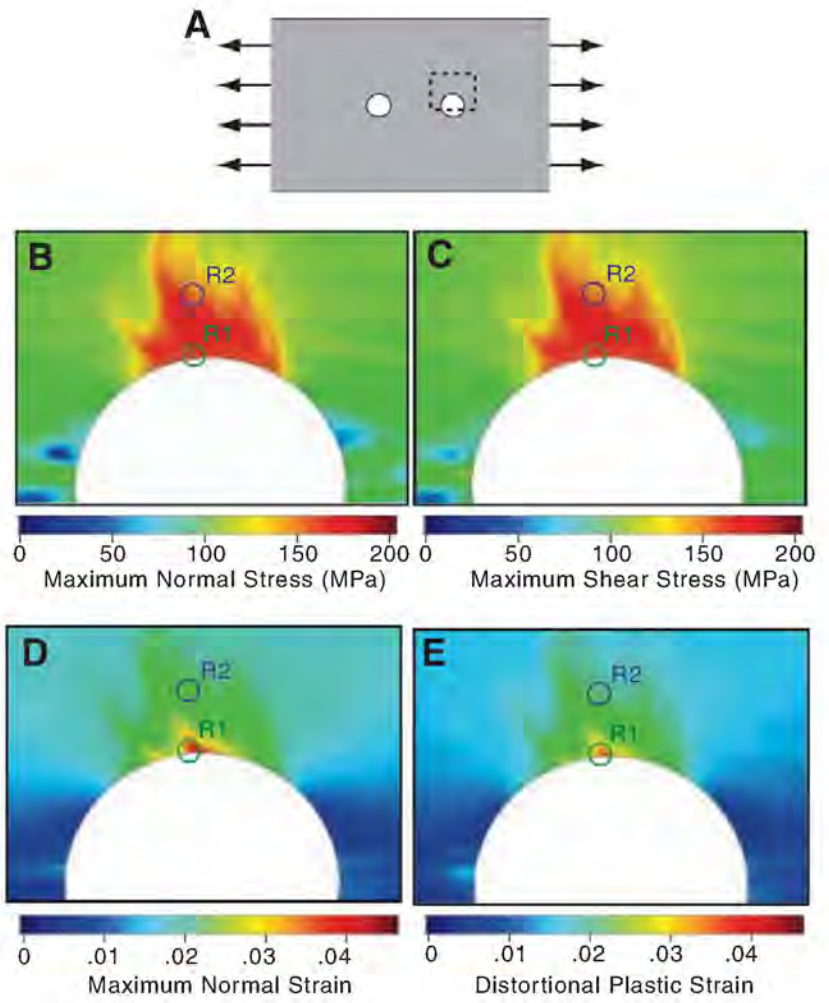


Fig. 1. Microfabrication techniques and electron beam evaporation were used to make thin-film tensile specimens with thicknesses ranging from 150 to 220 nm and mean grain sizes of 60 to 90 nm. The introduction of holes at horizontal (**A**) and angled orientations (**B**) produces complex stress and strain fields within the film when it is pulled in tension. Closer inspection of one of these holes in the TEM (**C**) shows submicrometer resolution at the hole edge and a microstructure that exists on a length scale orders of magnitude smaller than that associated with the sample geometry. Bright field TEM imaging at a higher magnification (**D**) shows a random microstructure with overlapping grains and high-angle grain boundaries.

Having clarified that the observed mechanical grain growth is driven by stress, we next investigated the relative importance of shear stresses in promoting this growth. Angled-hole specimens were studied to separate the regions where deformation is dominated by normal stresses from those where shear dominates. Our TEM observations were made after the specimen had undergone a complex deformation path; selecting stresses as the variables of interest would ignore previous deformation history and nonmonotonic behavior, both of which are important when the specimen wrinkles. Accordingly, it is important to consider the overall contribution of the stresses over the duration of the test, which is captured by energy quantities that include the history of the stresses. Therefore, we analyzed the simulations of this geometry in terms of the cumulative contributions of volumetric and distortional energy density incurred by the specimen, with these quantities being directly related to the normal and shear stresses, respectively (*26*). As demonstrated by the FEA shown in Fig. 3, applying a remote displacement of 25 μm to the angled-hole specimen resulted in a substantial enhancement of the distortional energy density in the region between the holes, whereas the volumetric energy density in this region was not strongly magnified by the presence of neighboring holes. Of the three regions quantitatively investigated for these specimens (Fig. 3B), region 2 had the highest distortional energy density, whereas region 1 incurred a higher distortional energy

density than region 3. Volumetric energy densities in regions 2 and 3 were about the same but lower than in region 1 (Fig. 3C), whereas all three were substantially lower than the distortional values. Post-mortem TEM measurements of these regions are summarized in Fig. 3D, where grain size distributions for each region and the as-deposited material are presented as cumulative distribution plots (additional characterization parameters are available in table S1). Inspection of these distributions shows systematic differences in grain growth. The highest average grain size and, correspondingly,



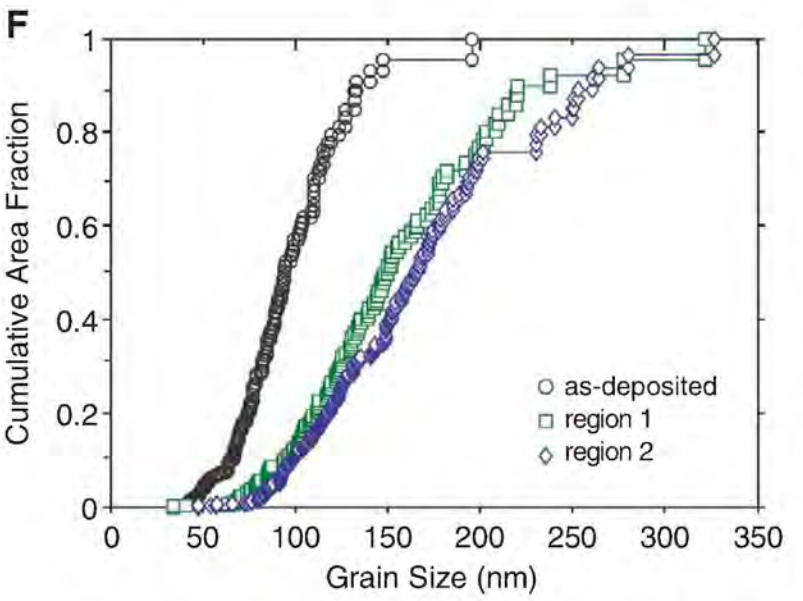
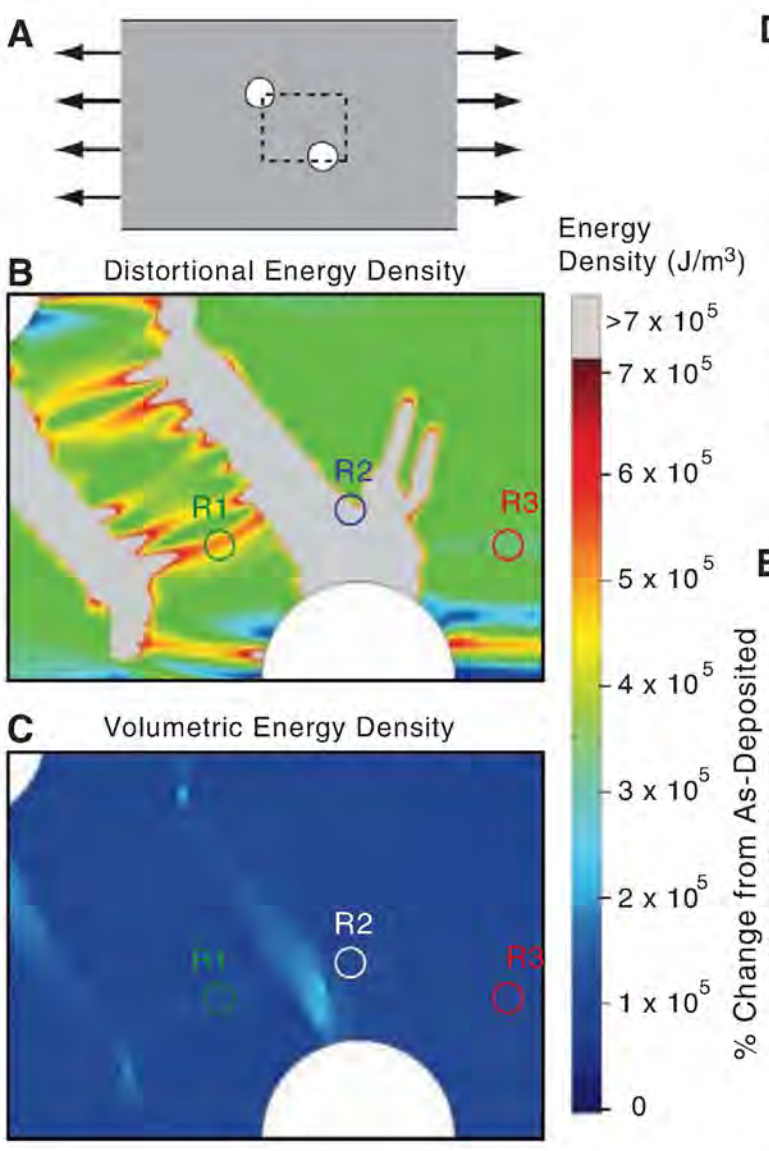


Fig. 2. Finite element simulations were used to investigate stress and strain fields in a region near the hole of a 170nm-thick horizontal-hole specimen (**A**). Contour plots of the maximum normal stress (**B**), maximum shear stress (**C**), maximum normal strain (**D**), and distortional plastic strain (**E**) are presented here. Regions of interest that were investigated in the TEM are denoted in the contour plots. The microstructure in each region was measured and compared with the as-deposited grain size distribution in the form of area-weighted cumulative distribution plots (**F**). Grain growth is highest away from the hole edge, showing that stress drives this microstructural evolution.



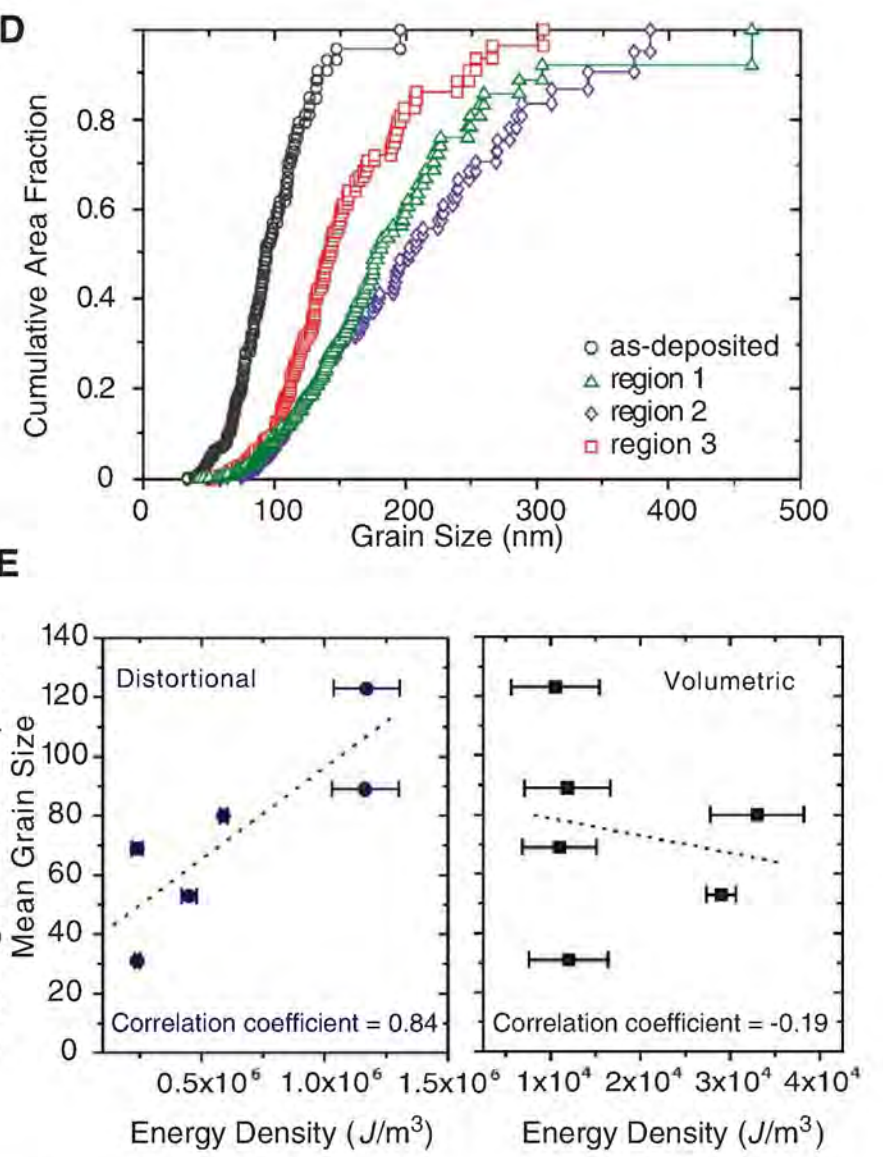


Fig. 3. The angled-hole geometry was modeled with finite element simulations to investigate the normal and shear stresses in the areas around and between the holes (**A**). The distributions of the distortional energy density (dominated by shear stresses) (**B**) and the volumetric energy density (dominated by normal stresses) (**C**) are presented by using contour plots. The gray areas represent areas where the energy density is higher than ~7×10^5 J/m^3. Regions of interest which were investigated in the TEM are denoted in the contour plots, with the microstructure in these regions presented as cumulative distribution plots of the area-weighted grain size (**D**). Correlations between energy density quantities and grain growth are examined (**E**), revealing a positive correlation between the extent of grain growth and distortional energy density, whereas no such relationship exists between grain growth and volumetric energy density. The error bars in (E) represent the standard deviation of the energy quantities from FEA over the regions where grain size statistics (~1000 grain sizes measured for these plots) were collected, whereas the dotted lines represent linear fits to the data to show general trends. These plots show that grain growth scales more closely with the trends in distortional energy density, pointing to shear stress as the driving force for the grain boundary migration during grain growth.

the most severe grain growth were measured in region 2, where only the distortional energy density term is the greatest. Direct comparison of regions 1 and 3 indicates that region 1 experienced markedly more grain growth than region 3. Taken as a whole, the measurements collected on multiple angled-hole specimens indicate that grain growth scaled with shear stresses that produce distortional work, with the grain size distribution displaying the most grain growth belonging to region 2, followed by region 1, and then region 3. By contrast, the hypothesis that normal stresses control grain growth would have predicted that growth in regions 2 and 3 would have been nearly the same and smaller than the growth in region 1, which is contrary to our observations. Figure 3E summarizes the results from two independent angled-hole specimens, with grain growth plotted versus the energy density terms. The dotted lines represent linear fits to the data, with the accompanying correlation coefficient for each fit provided at the bottom of the graph. From Fig. 3E, a positive correlation emerges between grain growth and distortional energy density, whereas grain growth does not appear to scale with increasing volumetric energy density. These results point to shear stress as the driving force for mechanically induced grain boundary migration.

Further insight into the mechanism of mechanical grain growth can be gained by analyzing changes in grain shape and the evolution of grain size distributions for the specimens discussed above as well as similar samples from slightly different deposition batches (*26*). Figure 4A shows that the aspect ratios of measured grains do not scale with the amount of growth experienced by the material. The fact that the grains remain essentially equiaxed (within the range of 1.3 to 1.5) precludes diffusion-controlled processes such as Coble creep (*27*). The grain growth observed in this study is also characterized by a grain size distribution that broadens as grain size increases (Fig. 4B), as opposed to a pure shift in the distribution toward larger grain sizes as would be expected for normal thermally driven grain growth (*28*) or the grain growth observed in superplastic deformation (*29*, *30*). Evidence for inhomogeneous growth, where certain grains grow preferentially at the expense of others, can also be found in the combined cumulative distribution plots (Figs. 2F and 3D). The finding that all of the grain size distributions start at the same minimum size indicates that small grains still exist within the evolved microstructure, although they represent a decreasing fraction of the material as grain growth progresses.

Although traditional grain growth mechanisms fail to explain the grain growth characterized in this study, the finding that grain growth scales with applied stress is in agreement with recent theoretical descriptions and molecular dynamics simulations (*13*, *14*) of coupled grain boundary migration. Snapshots of local tilt boundary behavior during the molecular dynamics simulations suggest that distortions of structural units consisting of only a few atoms produce the shear and attendant normal boundary motion. These simulations further illustrate that the coupling factor, β, which relates normal and tangential motion of a grain boundary, is geometrically related to the misorientation angle, even for high-angle boundaries (*14*). The original simulations focused on high-symmetry tilt boundaries (*13*, *14*), but more recent simulations suggest that the shear coupling occurs in more general boundaries as well (*31*, *32*, *21*). To date, experimental evidence of the coupling has been restricted to low- and high-angle tilt boundaries (*18*–*20*). The exact orientation of individual grains and grain boundaries could not be determined in the current study because there are multiple grains through the thickness of the film, but one advantage of the use of nanocrystalline samples lies in the fact that grain growth and, by inference, grain boundary migration were observed for a wide range of grain boundary characters. The finding that coupled boundary migration is not limited to tilt boundaries is especially intriguing.

This experimental confirmation of stress-driven migration of general grain boundaries is supported by recently published in situ TEM observations of ultrafast grain boundary motion in nanocrystalline (*12*) and ultrafine-grained Al (*33*). The in situ observations show the rapid motion of curved and nonspecific grain boundaries, but only under the influence of an applied stress. In situ measurements of the shear strain associated with grain boundary migration confirm the existence of a coupling factor in the case of a low-index grain boundary, but the measured values of this coupling were smaller than those predicted by Cahn. A more generalized geometric model of shear coupling, which is consistent with Cahn's model and with a grain boundary dislocation-based representation of grain boundary migration (*34*), has been derived to explain the in situ observations (*35*). The specific details of these coupled boundary migration models are still under debate, but the general conclusion of the current work, that shear stresses promote coupled grain boundary migration and grain growth in nanocrystalline Al, is fully consistent with all three geometric models.

The experimental finding that a general population of grain boundaries can be mobile during deformation contrasts with the generally accepted notion that grain boundaries act as stationary obstacles within a microstructure. Material scientists traditionally view the mechanics of grain boundaries in terms of the Hall-Petch relation (*1*, *2*), which states that a material's strength increases with decreasing grain size. The most common explanation of this trend describes grain boundaries as obstacles to the transfer of dislocations (and, therefore, plastic strain) between adjacent crystals. Although this is true for coarse-grained and microcrystalline materials, the grain boundary migration observed here demonstrates that grain boundaries in nanocrystalline materials can be responsible for a very different response, in fact accommodating plastic strain. The grain boundary motion itself represents a permanent transfer of material, with the lattice undergoing irreversible shear within the volume traversed by

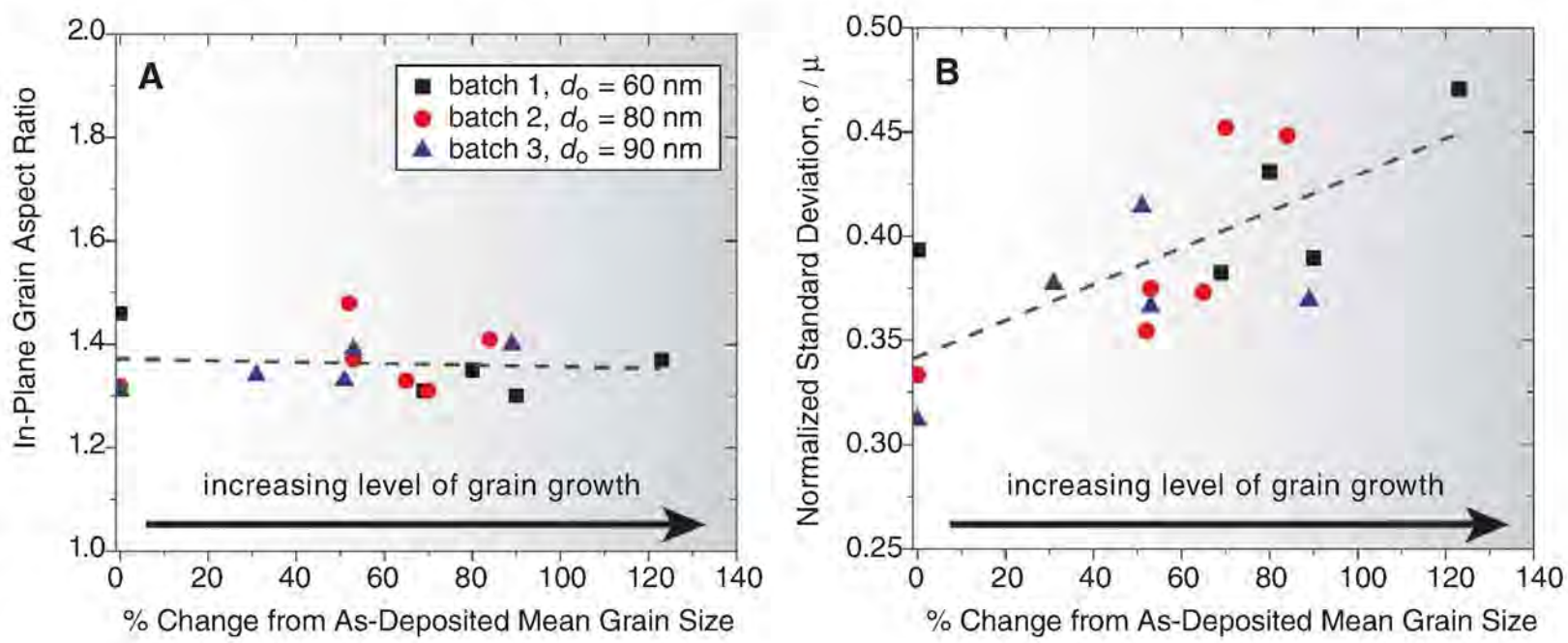


Fig. 4. Compilation plots quantifying the microstructural evolution observed in various specimens and specimen geometries (each data point represents over 100 grain size measurements). The labels batch 1, 2, and 3 represent different deposition batches with slightly different as-deposited average grain sizes (d_o = 60, 80, and 90 nm, respectively), whereas the dotted lines represent linear fits to the data points to show general trends. The aspect ratios of the grains do not change as a result of of grain growth (**A**). The normalized standard deviation increases with the level of grain growth (**B**), which is a signature of a grain size distribution that broadens as grain size increases. These results contrast with signatures of grain growth caused by thermal driving forces, diffusional creep, or superplastic deformation.

the boundary without the need for dislocation slip events. In addition to acting as a direct mechanism for plastic flow, coupled grain boundary migration creates larger grains within the microstructure, which allows microscale plasticity mechanisms (normal dislocation plasticity) to become active (*8*).

Having pinpointed shear stress as the driving force governing mechanically induced grain growth, it is worth asking what role stress-driven grain boundary migration plays in governing materials behavior. The microstructural instability noted in nanocrystalline materials (*3*–*12*) indicates that grain boundary migration can result in mechanical behavior that is not only different from microcrystalline materials but dynamic as well. This departure from conventional plasticity is no doubt associated with the high stresses that nanocrystalline metals can accommodate. In conventional polycrystalline materials, the onset of dislocation-based plasticity limits the stresses that can be applied; nevertheless, it is reasonable to conclude that there may be hereto overlooked situations where stress-driven boundary migration influences the mechanical response and microstructural stability of other materials as well.

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Real-Time Observation of Carbonic Acid Formation in Aqueous Solution

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Despite the widespread importance of aqueous bicarbonate chemistry, its conjugate acid, carbonic acid, has remained uncharacterized in solution. Here we report the generation of deuterated carbonic acid in deuterium oxide solution by ultrafast protonation of bicarbonate and its persistence for nanoseconds. We follow the reaction dynamics upon photoexcitation of a photoacid by monitoring infrared-active marker modes with femtosecond time resolution. By fitting a kinetic model to the experimental data, we directly obtain the on-contact proton-transfer rate to bicarbonate, previously inaccessible with the use of indirect methods. A Marcus free-energy correlation supports an associated pK_a (K_a is the acid dissociation constant) of 3.45 ± 0.15, which is substantially lower than the value of 6.35 that is commonly assumed on the basis of the overall carbon dioxide–to–bicarbonate equilibrium. This result should spur further exploration of acid-base reactivity in carbon dioxide–rich aqueous environments such as those anticipated under sequestration schemes.

Recent isolation of carbonic acid (H_2CO_3) in the gas and solid phases has conclusively disproved long-held claims of the molecule's intrinsic kinetic instability (*1*–*3*). Theoretical calculations have shown that H_2CO_3 only becomes unstable when water is present; that is, adding a single water molecule to anhydrous H_2CO_3 accelerates its simulated decomposition by a factor of 10^9 (*4*–*9*). Aqueous H_2CO_3 is understood to dissociate by a proton-relay mechanism that uses several catalyzing water molecules. For this reason, direct observation of aqueous H_2CO_3 has proven to be elusive, a situation that is somewhat surprising given the vital physiological role that the H_2CO_3/HCO_3^- buffer system has long been known to play in regulating the pH of blood and other biological fluids (*10*). Furthermore, sequestration plans to mitigate anthropogenic carbon dioxide emissions involve injecting several hundreds of gigatons of CO_2 into the oceans (*11*). Precise and reliable dissociation constants for carbonic acid over a wide range of ionic strengths, temperatures, and pressures will need to be established to determine in situ chemical behavior in such contexts (*12*–*14*).

In pure water (pH = 7 before CO_2 dissolution), aqueous solvation of CO_2 is understood to be accompanied by hydration, resulting in carbonic acid (H_2CO_3) (Eq. 1), and subsequent acid-base chemistry leading to bicarbonate (HCO_3^-) and carbonate (CO_3^{2-}) (Eq. 2)

$$CO_2(g) + 3H_2O \rightleftarrows CO_2(aq) + 3H_2O \rightleftarrows H_2CO_3 + 2H_2O \quad (1)$$

$$H_2CO_3 + 2H_2O \rightleftarrows HCO_3^- + H_3O^+ + H_2O \rightleftarrows CO_3^{2-} + 2H_3O^+ \quad (2)$$

The net result is a decrease in pH. Conversely, bicarbonate acts as a moderately weak base in solutions below neutral pH; titrations on time scales extending to minutes afford an effective pK_a (K_a is the acid dissociation constant) value

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of 6.35, as represented by the reaction in Eq. 3 (*15*, *16*)

$$CO_2(aq) + 2H_2O \rightleftarrows HCO_3^- + H_3O^+ \quad (3)$$

It is important to note, however, that the nature of the conjugate acid $CO_2(aq)/H_2O$ is ill-defined, because the reactions in both Eqs. 1 and 2 participate in the chemistry. The true pK_a of carbonic acid would characterize the first equilibrium of Eq. 2, independent of the (de)hydration and (de)solvation reactions in Eq. 1. The value of the true acid dissociation constant of carbonic acid is connected to the effective value for $CO_2(aq)$ by the relation $K_a(H_2CO_3) = K_a(CO_2(aq)) \cdot (1 + [CO_2]/[H_2CO_3])$ (*15*) and may be found if the concentration ratio of CO_2 to H_2CO_3 is known. This ratio is usually assumed to have a value of several hundreds, implying concentrations of H_2CO_3 in water larger than 10^{-8} M, and $pK_a(H_2CO_3) \approx [pK_a(CO_2(aq)) - 2] \approx 4$. However, because the compound has so far eluded a direct detection, the true pK_a value and its associated implications for reactivity have been specified with large uncertainty (*16*, *17*).

Many earlier efforts to characterize the kinetics of aqueous carbonic acid have relied on indirect relaxation methods, including isotope exchange, temperature change, and pH-jump measurements, with limited temporal resolution (*18*, *19*). For example, determination of H_2CO_3 in time-resolved experiments by rapid mixing of $CO_2(aq)$ and a basic solution is difficult to achieve, because the kinetics of the forward reactions of Eq. 1 are dominated by the slowest step, namely hydration of $CO_2(aq)$ resulting in H_2CO_3. The ensuing dissociation of H_2CO_3 into H_3O^+ and HCO_3^- (Eq. 2) then leads to rapid depletion of H_2CO_3, precluding a substantial transient population build-up. The reverse reaction, involving transient protonation of HCO_3^-, could potentially lead to substantial generation of H_2CO_3. However, previous studies of the protonation reaction dynamics of HCO_3^- relied on stopped-flow techniques with insufficient time resolution for transient observation of the acid (*20*–*22*).

We overcame these challenges through the use of a photoacid that is optically triggered to transfer a proton to HCO_3^- on ultrafast time scales (Fig. 1). A photoacid exhibits a strong change in its pK_a value upon electronic excitation (*23*, *24*), enabling dynamical studies of processes with femtosecond time resolution, such as protonation of bases present in the same solution (*25*–*29*). We follow the progress of the photoinduced reaction by monitoring infrared (IR)–active marker modes of the photoacid, its conjugate photobase, and carbonic acid in D_2O. Solutions buffered at pD = 8 are used to prevent slow decomposition of DCO_3^- during the measurements. 2-Naphthol-6,8-disulfonate (2N-6,8S) is used as photoacid because it has the required properties (ground state $pK_a = 9.3$ to 9.4, excited state $pK_a = 1.0$ to 1.3 in D_2O at 0 M ionic strength) for excited-state deuteron transfer to DCO_3^- ($pK_a \approx 4$ for D_2CO_3). We optimized the working conditions (50 mM 2N-6,8S, 0.1 to 0.8 M DCO_3^-, 0.15 M TRIS/DCl as buffer dissolved in 100 ml solutions of D_2O) to ensure that changes in the solution caused by CO_2 loss remained moderate. To ensure that the changes did not affect the measured signal, we monitored the pD of the solution and the changes in relative concentration of photoacid and conjugate photobase before, during and after the measurements (figs. S1 and S3) (*19*).

Because we needed high concentrations (0.1 to 0.8 M) of the accepting base DCO_3^- to perform photoinduced diffusion-assisted bimolecular neutralization experiments, we were restricted to probing IR marker modes in spectral regions not rendered opaque by the DCO_3^- vibrational transitions, located at 1366 and 1628 cm^{-1} (Fig. 2A). The steady-state IR spectra of 2N-6,8S in the electronic ground state indicate that, throughout the fingerprint region, the vibrational mode patterns depend strongly on whether 2N-6,8S is in its photoacid or photobase configuration (Fig. 2B). In the transient pump-probe spectra, two spectrally resolved vibrational marker modes, with frequencies of 1472 and 1510 cm^{-1}, could be assigned, respectively, to the photoacid and photobase configurations of 2N-6,8S in its first electronic excited state (Fig. 2C). As a result, it was possible to monitor the decay of the 1472-cm^{-1} photoacid band and the corresponding rise of the photobase band at 1510 cm^{-1} as an unambiguous probe of the primary event of deuteron transfer, when 2N-6,8S releases its deuteron to either the solvent or to an accepting base (Fig. 2D). The 1410-cm^{-1} photobase band appeared to overlap spectrally with a carbonic acid band and, thus, could not be used to derive deuteron-transfer dynamics.

In addition, we observed the rise of a band at 1720 cm^{-1}, well within the frequency range where carbonyl stretching modes typically appear. This band position is in full accordance with the frequencies ranging from 1705 to 1730 cm^{-1} that have been reported in the literature on carbonic acid formed by high-energy irradiation of CO_2/water-ice mixtures (*30*–*32*), by proton irradiation of pure solid CO_2 or CO_2/water-ice mixtures (*31*, *32*), in protonated HCO_3^- embedded in ice matrices (*2*), on calcium carbonate surfaces reacting with SO_2 or HNO_3 in the presence of water (*33*), and with theoretical calculations (*34*). Theoretical results suggest that the vibrational bands observed in the solid and gas phase are actually due to H_2CO_3 dimers (*35*). Under our experimental conditions, involv-

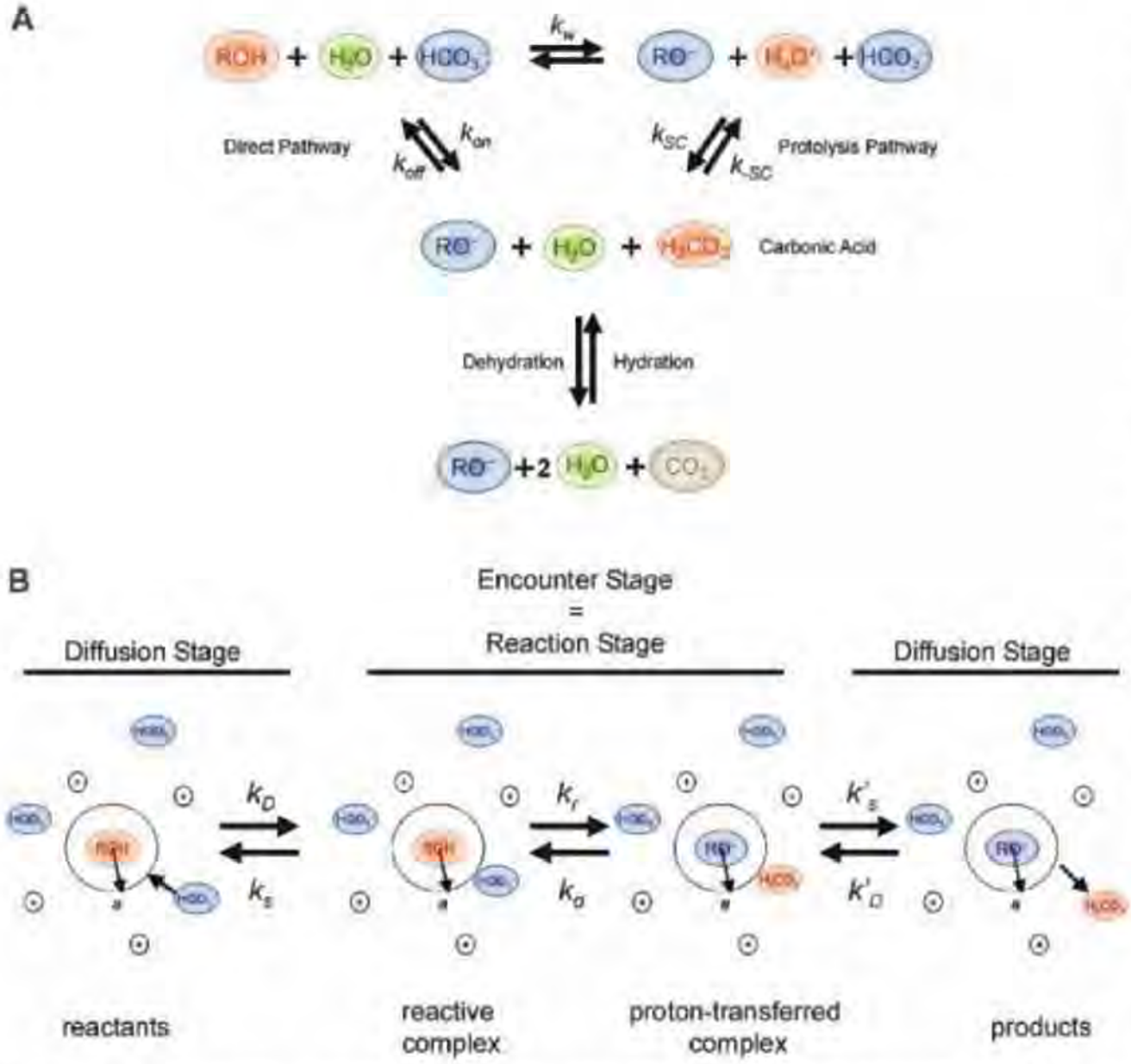

Fig. 1. (**A**) Reaction pathways between an organic acid and bicarbonate adapted from Eigen's scheme for acid-base neutralization (*22*). The hydrolysis and hydroxide addition pathways are omitted here for greater clarity, as these do not play a major role under our experimental conditions. (**B**) The diffusion and reaction stages of the direct pathway, explicitly taken into account in our diffusion-assisted bimolecular proton-transfer modeling. The reaction pair encounter distance is indicated with the symbol *a*.

ing ultrafast protonation of a base diluted in a polar solvent (D_2O), such dimers are not expected to be prominent. Based on the fact that we detect a product species with a vibrational marker mode located at a frequency typical for carbonyl stretching, we can exclude the generation of a zwitterionic structure (i.e., D_2O^+-COO^-) that could not be excluded as a potential intermediate in previous time-resolved studies of bicarbonate dehydration (*20*). Furthermore, in an experiment with 0.1 M DCO_3^-, we have been able to observe a correlation between the DCO_3^- marker-band decay and the D_2CO_3 marker-band rise, from which we ascertain that the D_2CO_3 marker band is an unequivocal probe for the final deuteron transfer to the accepting base (Fig. 3). We also performed two experiments using either $D^{12}CO_3^-$ or $D^{13}CO_3^-$ as accepting bases under identical conditions. We detected a frequency shift of the rising marker mode that matches known values for isotope shifts when comparing the C=O stretching mode of $D_2{}^{12}CO_3$ with that of $D_2{}^{13}CO_3$ (*36*, *37*). In addition, the ratio of the magnitude of DCO_3^- bleach and D_2CO_3 signal is in full accordance with reported values (*2*), indicating that the quantity of D_2CO_3 produced corresponds to the quantity of DCO_3^- lost.

We did not detect any transient signals in the region around 2364 cm^{-1} where the asymmetric stretching marker mode of CO_2 appears; thus, no substantial dehydration of D_2CO_3 to CO_2 occurs on subnanosecond time scales. Instead, D_2CO_3 appears to be a kinetically stable compound with a lifetime extending well beyond 1 ns, the maximum scanning range of our delay stage.

In the concentration range employed (0.1 to 0.8 M $NaDCO_3$; the maximum concentration that can be achieved for the buffered solutions, which have ionic strengths similar to that found in the oceans), neither the rise of the photobase marker band at 1510 cm^{-1} nor the rise of the D_2CO_3 marker band at 1720 cm^{-1} showed time-resolution–limited dynamics. Hence, we can exclude a prompt deuteron transfer away from the electronically excited photoacid, as well as subpicosecond deuteron transfer to the base. Previous results obtained for deuteron transfer from pyranine [8-hydroxy-pyrene-1,3,6-trisulfonate (HPTS)] to a family of carboxylate bases showed kinetics driven by a substantial fraction of on-contact reactive complexes, in which the photoacid and the base are directly linked, or else bridged by only a single water molecule (*26*–*28*). However, it appears here that on-contact reactive complexes, present at the moment of electronic excitation of the photoacid, are of minor importance. This may be because much lower concentrations were used in the present experiment on account of the lower solubility of sodium bicarbonate. Moreover, the relatively slow effective deuteron transfer could be a strong indication that in the acid-base neutralization of 2N-6,8S and DCO_3^-, the reactive encounter complex probably contains several water solva-

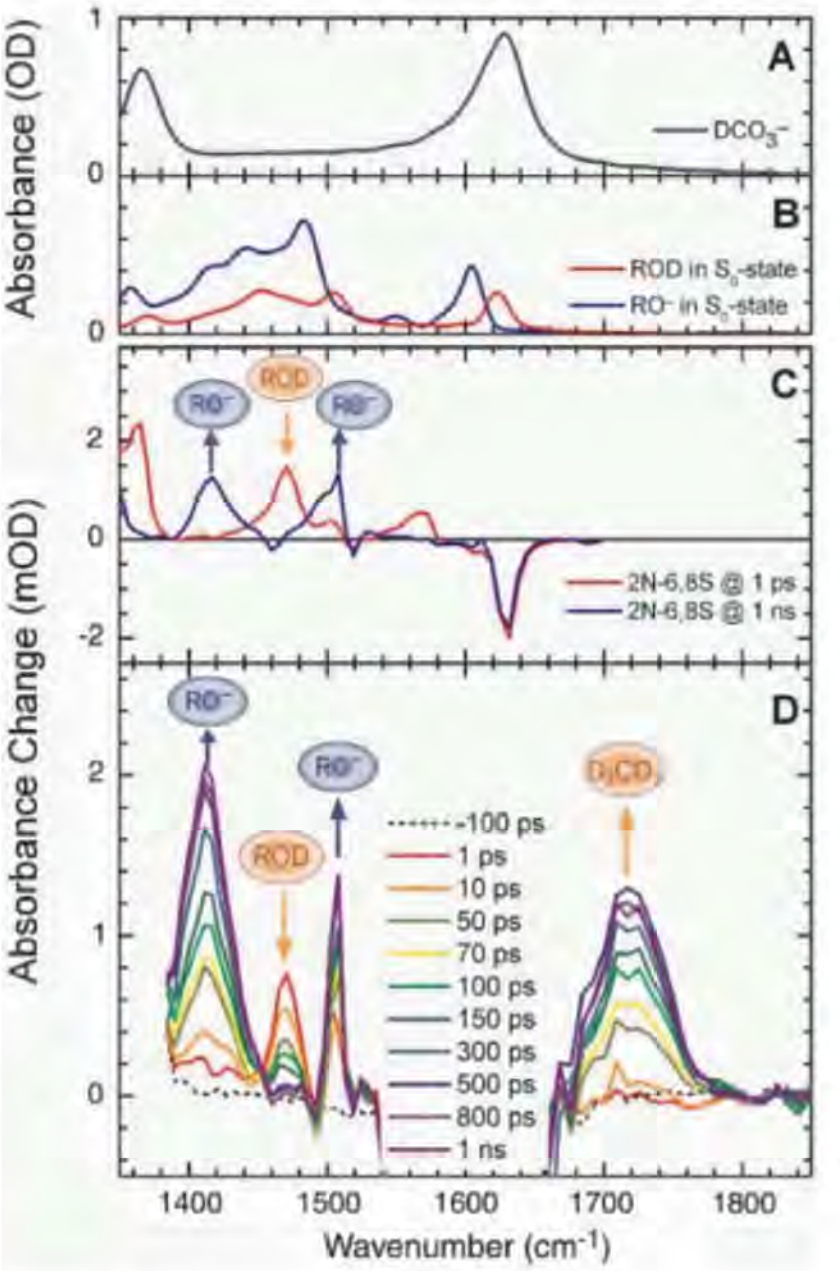

Fig. 2. (**A**) Experimental steady-state IR spectrum of $NaDCO_3$ in D_2O. (**B**) Steady-state IR spectra of 2N-6,8S in D_2O at pD = 1 (red curve) and pD = 12 (blue curve) showing the fingerprint modes of electronic ground state 2N-6,8S in the photoacid (ROD) and photobase (RO^-) forms, respectively. (**C**) Transient IR difference spectra measured for 2N-6,8S at pD = 5 in ROD form at a pulse delay of 1 ps (red curve) and after conversion into the RO^- form at a pulse delay of 1 ns (blue curve), showing bleach signals of fingerprint vibrations of ROD in the ground state and positive absorbance signals marking vibrations in the electronically excited state for both the ROD and RO^- forms. (**D**) Transient IR spectra of the neutralization reaction between 2N-6,8S and 0.5 M DCO_3^- measured at the probe pulse delays indicated in the legend, showing the marker modes of electronically excited 2N-6,8S in the ROD (1472 cm^{-1}) and RO^- (1410 and 1510 cm^{-1}) forms and of D_2CO_3 at 1720 cm^{-1}. OD, optical density.

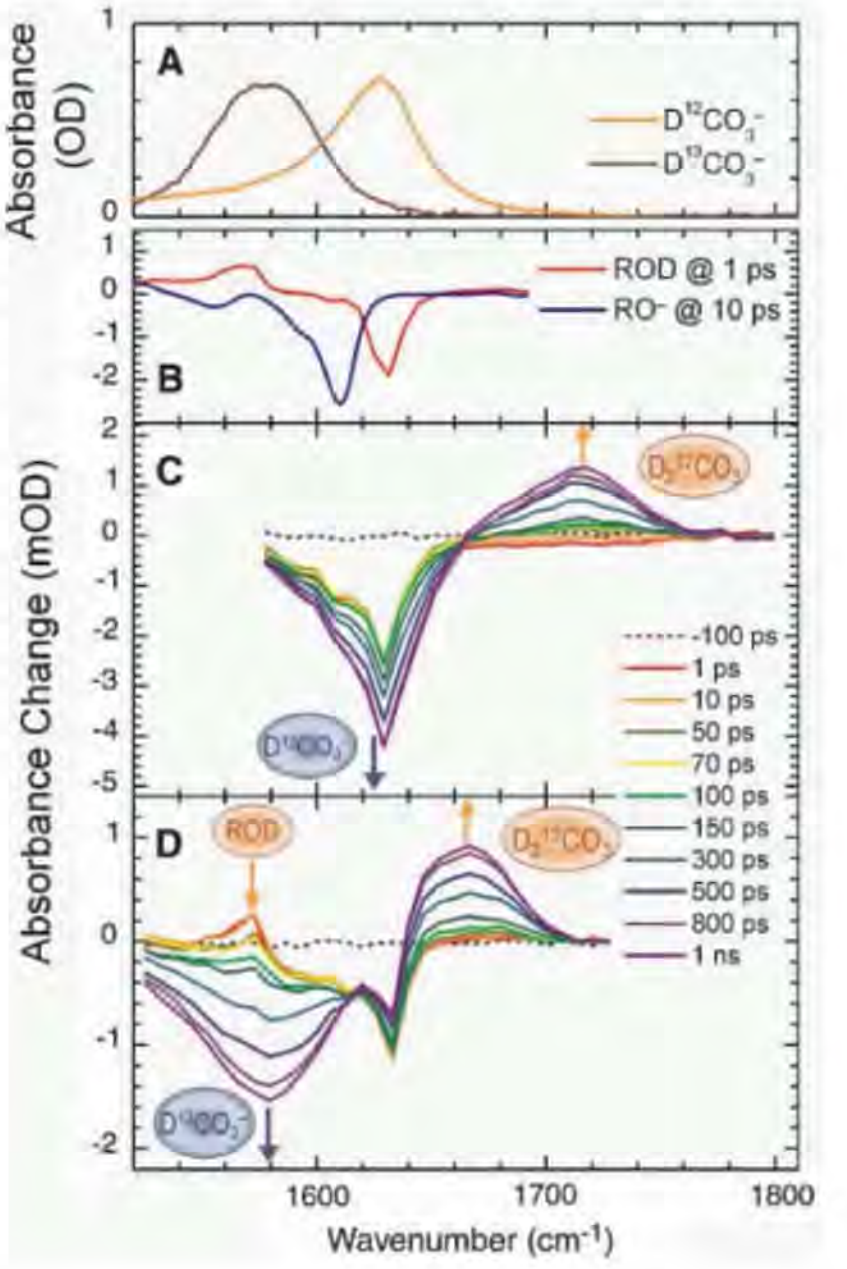

Fig. 3. (**A**) Steady-state IR spectrum of $D^{12}CO_3^-$ and $D^{13}CO_3^-$. (**B**) Transient IR difference spectrum of electronically excited 2N-6,8S in ROD (red curve) and RO^- (blue curve) forms, together with bleach signals corresponding to the ROD (1632 cm^{-1}) or RO^- species in the electronic ground state, generated within instrument-limited temporal resolution. (**C**) Kinetic measurement using 0.1 M $D^{12}CO_3^-$ showing the correlated bleach increase at the $D^{12}CO_3^-$ marker mode (1628 cm^{-1}) and the rise of the $D_2{}^{12}CO_3$ C=O stretching marker band (1720 cm^{-1}). (**D**) Kinetic measurement using 0.1 M $D^{13}CO_3^-$ showing the correlated bleach increase at the $D^{13}CO_3^-$ marker-mode frequency (1579 cm^{-1}) and the rise of the $D_2{}^{13}CO_3$ C=O stretching marker band (1666 cm^{-1}).

tion shells separating acid and base, whereas the proton transfer occurs on picosecond time scales. Similar results were obtained in a recent study of the acid-base neutralization of 2N-6,8S with cyanate performed with comparable base concentrations (*19*).

We have analyzed the transient spectra (Fig. 2D) recorded for three concentrations of DCO_3^- using a line-shape fitting routine to extract the kinetics of the vibrational marker bands (*19*). Briefly, bleach signals indicating marker bands of the photoacid or photobase in the S_0 state show no dynamics on the time scale of the experiment. Marker bands of the photoacid in the S_1 state decay with identical temporal characteristics to those with which the marker bands of the photobase in the S_1 state increase in magnitude. These two types of marker bands indicate the event of deuteron release from the photoacid (converting into the photobase) to possible accepting water solvent molecules (protolysis pathway of Fig. 1) or to the bicarbonate base (direct proton-transfer pathway of Fig. 1). The delayed deepening of the DCO_3^- bleach and the rise of the D_2CO_3 marker bands indicate binding of the deuteron at the base. The slower dynamics of these marker bands compared with those of the photoacid/photobase bands are a signature of deuterons temporarily residing on water (*26*, *27*). In Fig. 4, we display the time-dependent decay of the photoacid 1472 cm^{-1} band and the rise of the photobase band at 1510 cm^{-1} and of the carbonyl stretching band of D_2CO_3 at 1720 cm^{-1}. The nonexponential growth behavior of these latter marker bands, as well as the decay of the photoacid band at 1472 cm^{-1}, is governed by the time-dependent concentration gradient of the DCO_3^- base around the photoacid, which approaches a steady-state value at long times. The early time components are due to the reaction of 2N-6,8S with DCO_3^- in close proximity, involving minimal earlier mutual diffusion of the two reaction partners (*38*). The signals at longer pulse delays are due to acid and base reacting after substantial molecular diffusion toward each other. We have used an analytical framework derived by Szabo (see Fig. 1B) to describe the diffusion-controlled (time-dependent) reaction dynamics between 2N-6,8S and DCO_3^- under finite ionic strength (*19*, *39*). The resulting simulated reaction kinetics fit to the spectroscopic data are shown as solid lines in Fig. 4.

We extract from the simulations a deuteron-transfer time of 8.6 ps upon formation of photoacid-base encounter complexes, implying even shorter times for proton transfer. The ultrafast proton-transfer rate $k_r = (6\ ps)^{-1} = 1.7 \cdot 10^{11}\ s^{-1}$ is about five times faster than the overall diffusion-limited rate constant that is calculated with similar values for the ionic strength. Thus, in a real-time experiment, we uncover details of the reaction dynamics that are unattainable with the experimental methods previously reported (*19*). In particular, a bimolecular (time-independent) rate constant of $k_{on} = 4.7 \cdot 10^{10}\ M^{-1}\ s^{-1}$ for the proton transfer to bicarbonate was reported by Eigen *et al.* with the use of indirect relaxation techniques (*20*, *22*). The measured reaction rate was found to be diffusion-limited, in accordance with our findings on the ultrafast (albeit finite) reaction rate of the encounter complex. In Fig. 4D, we compare the first-order protonation rate k_r in the encounter complex with previously reported results obtained from acid-base neutralization experiments of HPTS by carboxylate bases (*26*–*28*, *40*). We used the Marcus free-energy correlation for aqueous proton transfer (*19*, *41*) to plot the overall proton-transfer rate of the encounter complex as a function of ΔpK_a, defined as the difference between pK_a(photoacid in S_1 state) and pK_a (conjugate acid of accepting base). After correcting our measured rate for D/H isotope substitution (*19*), we found that the correlation holds for a carbonic acid pK_a of 3.45 ± 0.15, as opposed to the widely used effective pK_a of 6.35 for $CO_2(aq)/H_2O$. This result follows naturally from the real-time observation of proton transfer to bicarbonate on the picosecond time scale, without interfering effects from slower reversible deprotonation or dehydration reactions of carbonic acid.

Our work has clearly demonstrated that, in aqueous solution, D_2CO_3 is kinetically stable compared with its formation rate and that the dehydration rate of D_2CO_3 is relatively slow. Taking into account the combined effects of mutual diffusion (with forward k_D and backward k_s diffusion-controlled rates, respectively) and the proton transfer within the encounter complex (with forward k_r and backward k_d on-contact rates, respectively) (*38*), the deprotonation reaction rate constant (k_{off}) of D_2CO_3 (and, hence, the effective lifetime of the acid) at room temperature may be estimated from the measured overall deuteration rate of DCO_3^- anion, scaled to zero ionic strength, and the equilibrium acid dissociation constant of D_2CO_3: $k_{off} = K_a \cdot k_{on} = 10^{-pKa}\ M \cdot k_D k_r/(k_s + k_r)\ M^{-1}\ s^{-1} = 10^{-4}\ M \cdot 3.3 \cdot 10^{10}\ M^{-1}\ s^{-1} = 3.3 \times 10^6\ s^{-1}$. Here we have used the relation $pK_a(D_2CO_3) \approx pK_a(H_2CO_3) + 0.5$ (*15*). This rate constant corresponds to a lifetime of ~300 ns for D_2CO_3 before deuteron dissociation ensues. Therefore, from a kinetic point of view, the main cause of instability of D_2CO_3 over short times under aqueous conditions is acid

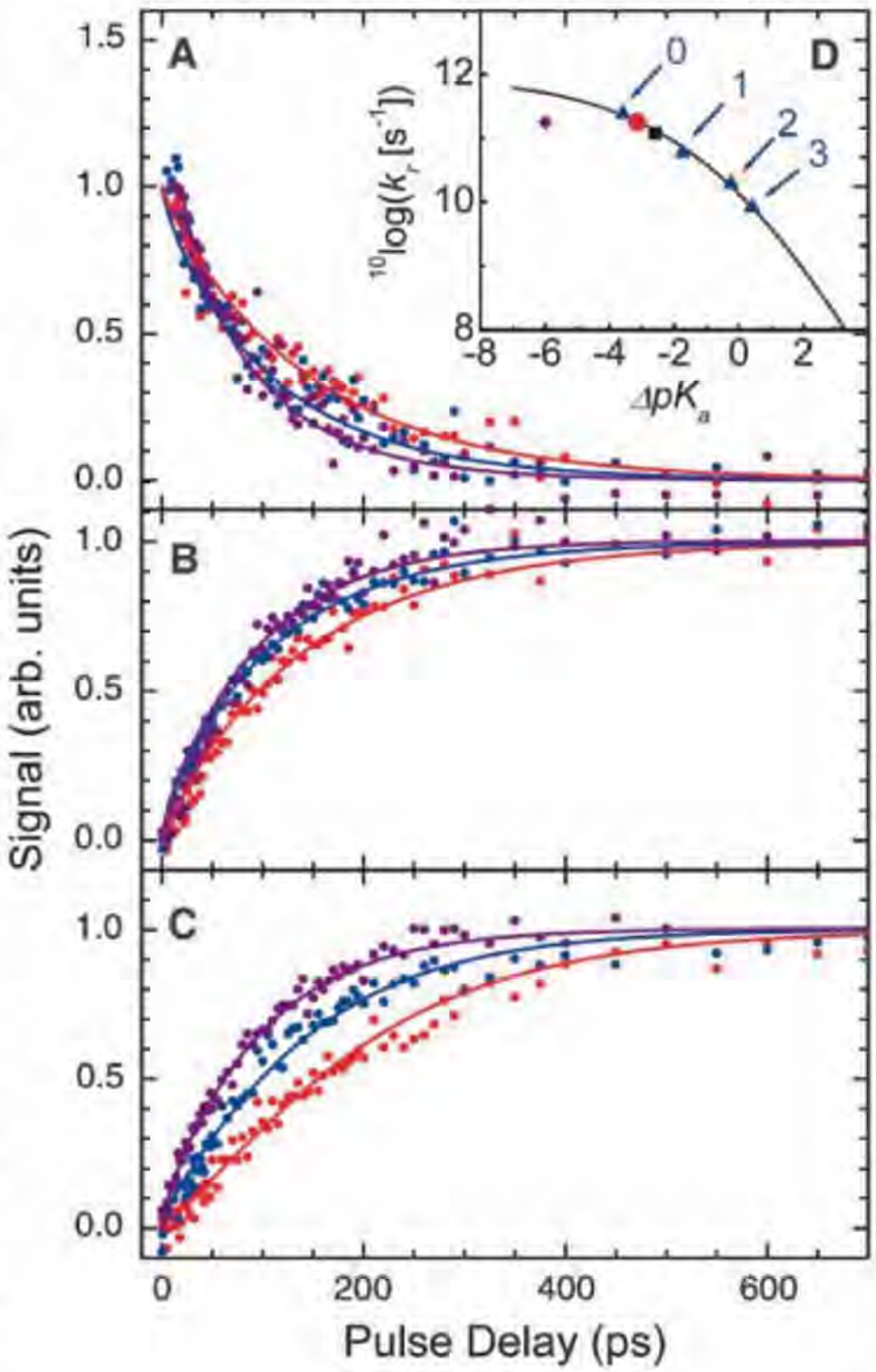

Fig. 4. Kinetics of the photoacid marker mode at 1472 cm^{-1} (**A**), the photobase transition at 1510 cm^{-1} (**B**), and the D_2CO_3 carbonyl stretching vibration at 1720 cm^{-1} (**C**) for three concentrations of DCO_3^- base: (i) 0.25 M (red dots), (ii) 0.5 M (blue dots), and (iii) 0.8 M (purple dots). Solid lines are fits with the use of the diffusion-assisted bimolecular reaction model described in the text. The free-energy correlation connecting ΔpK_a (acid-base) to the overall proton transfer in the encounter complex k_r is shown in (**D**). Blue triangles denote the acid-base neutralization reactions between HPTS and $CH_{3-x}Cl_xCOO^-$ (x = 0 to 3, as indicated with arrows), the black square indicates the reaction between HPTS and $HCOO^-$, the red dot denotes the reaction between 2N-6,8S and bicarbonate described here using a pK_a value of 3.45. For comparison, the purple diamond indicates where the point would appear using the effective pK_a value of 6.35.

dissociation (deprotonation), rather than decomposition into CO_2 and H_2O, which takes place with an effective rate constant of $1.8 \cdot 10^1\ s^{-1}$ (*18*). This conclusion also holds for H_2CO_3, though the opposite is still commonly asserted by chemistry textbooks (*5*, *42*). Carbonic acid acts like an ordinary carboxylic acid on nanosecond time scales with an acidity comparable to that of formic acid. This considerable acidity of carbonic acid should henceforth be considered in the context of CO_2-rich aqueous environments. In particular, potential surface and deep-sea interfacial chemical reactivity of intact H_2CO_3 with solid substrates remains uncharted.

By comparing the magnitude of the D_2CO_3 signal at long pulse delays with the DCO_3^- bleach signal and using the known value for the extinction coefficient of DCO_3^- ($933.5\ M^{-1}\ cm^{-1}$), we can derive a cross section of $750 \pm 50\ M^{-1}\ cm^{-1}$ for the C=O stretching mode of aqueous carbonic acid, which is comparable to that of carboxylic acids. This cross section should be sufficient to facilitate time-resolved IR studies of carbonic acid generation, deprotonation, and dehydration dynamics in biophysical systems. Probing the reaction dynamics of Eqs. 1 and 2 in the forward and backward directions as a function of ionic strength, temperature, and pressure will help in the determination of the reaction equilibrium constants under conditions that are relevant for the global carbon cycle.

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Supporting Online Material

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SOM Text
Figs. S1 to S5
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Bacterial Community Variation in Human Body Habitats Across Space and Time

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Elucidating the biogeography of bacterial communities on the human body is critical for establishing healthy baselines from which to detect differences associated with diseases. To obtain an integrated view of the spatial and temporal distribution of the human microbiota, we surveyed bacteria from up to 27 sites in seven to nine healthy adults on four occasions. We found that community composition was determined primarily by body habitat. Within habitats, interpersonal variability was high, whereas individuals exhibited minimal temporal variability. Several skin locations harbored more diverse communities than the gut and mouth, and skin locations differed in their community assembly patterns. These results indicate that our microbiota, although personalized, varies systematically across body habitats and time; such trends may ultimately reveal how microbiome changes cause or prevent disease.

The human body hosts complex microbial communities whose combined membership outnumbers our own cells by at least a factor of 10 (*1*, *2*). Together, our ~100 trillion microbial symbionts (the human microbiota) endow us with crucial traits; for example, we rely on them to aid in nutrition, resist pathogens, and educate our immune system (*1*, *3*). To understand the full range of human genetic and metabolic diversity, it is necessary to characterize the factors influencing the diversity and distribution of the human microbiota (*4*, *5*).

Determining our microbiota's role in disease predisposition and pathogenesis will depend critically upon first defining "normal" states (*5*). Prior studies of healthy individuals have focused on particular body habitats including the gut (*6*, *7*), skin (*8*–*10*), and oral cavity (*11*, *12*), and have revealed microbial communities that were highly variable both within

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and between people. However, our microbial habitats are not isolated from one another; instead, each person comprises a complex, yet interconnected landscape, consisting of many body habitats harboring distinctive microbiotas (*1*). We currently lack an integrated "whole-body" view of the microbial communities associated with healthy people over time.

Here, we address three general questions regarding the biogeography of the human microbiota in healthy adults: How is bacterial diversity partitioned across body habitats, people, and time? How does diversity at a variety of skin locales compare to that found in other body habitats? Do skin communities assemble differently at different sites? We performed an intensive survey of human-associated bacterial communities using a multiplexed barcoded pyrosequencing approach. Microbiota samples were donated on 17 and 18 June and 17 and 18 September 2008. Volunteers were unrelated individuals of both sexes (*13*), and the following body habitats were sampled: gut (stool), oral cavity, external auditory canal [EAC; including earwax (cerumen) if present], inside the nostrils (nares), hair on the head, and skin surfaces (fig. S1). Up to 18 skin locations were sampled on each day, and we subsequently performed a skin community assembly experiment. For each sample, variable region 2 (V2) of the bacterial 16*S* ribosomal RNA (rRNA) gene was amplified by polymerase chain reaction using a primer set with a unique error-correcting barcode (*14*). Using this approach, we generated a data set consisting of >1,070,000 high-quality, classifiable 16*S* rRNA gene sequences with an average of 1315 ± 420 (SD) sequences per sample (n = 815; table S1).

The sequences collected for this study provide an overview of the healthy human microbiota. Across all body habitats we detected members of 22 bacterial phyla, but most sequences (92.3%) were related to four phyla: Actinobacteria (36.6%), Firmicutes (34.3%), Proteobacteria (11.9%), and Bacteroidetes (9.5%). Each habitat harbored a characteristic microbiota (figs. S2 to S4) and a relatively stable set of abundant taxa across people and over time (fig. S4) (*13*).

We assessed differences in overall bacterial community composition using a phylogeny-based metric, UniFrac (*15*). A relatively small UniFrac distance implies that two communities are similar, consisting of lineages sharing a common evolutionary history. UniFrac-based principal coordinates analysis (PCoA) revealed strong primary clustering by body habitat, rather than by host sex, individual, or day (Fig. 1 and fig. S5). Moreover, hierarchical clustering of UniFrac- and phylotype-based distances (phylotypes defined at ≥97% sequence identity; fig. S6) revealed a nested structure, with communities grouping first by body habitat, then by host individual, and finally by month. Accordingly, we found that composition varied significantly less within habitats than between habitats. Within habitats, variation was significantly less within individuals sampled over time than between individuals on a given day. Finally, after accounting for habitat and host individual, variation was significantly less over 24 hours than over 3 months ($P < 0.01$ for each comparison, one-tailed t tests; Fig. 1E and fig. S7). Hierarchical clustering of UniFrac distances among people's daily composite "whole-body" communities (as defined with respect to our study) revealed perfect grouping by host individual and month (fig. S8), further emphasizing that our seemingly personalized microbiota remains relatively stable over time.

Despite the strong inter- and intrapersonal structuring of bacterial diversity, a high degree of spatial and temporal variability was also evident. We estimated community overlap by examining the fraction of shared phylotypes and evolutionary history (i.e., branch length) within a phylogenetic tree. Study-wide, ~12% of phylotypes (20% of branch lengths) appeared on all dates, whereas 3% of phylotypes (9% of branch lengths) appeared in all individuals, and only 0.1% of phylotypes (1% of branch lengths) appeared in all body habitats (fig. S9). No dominant phylotype was distributed among all of the body habitats of any person on any given day at our level of survey effort.

Body habitats differed in the degree to which their bacterial communities exhibited compositional variation. Although intrapersonal differences (over time) were smaller than interpersonal differences (on each day) within all habitats examined (Fig. 1F and fig. S10), oral cavity communities were significantly less variable in terms of membership alone, both within and between people, than all other habitats ($P < 0.01$ for each comparison, one-tailed t tests; Fig. 1F and fig. S10A). Gut community structure was highly var-

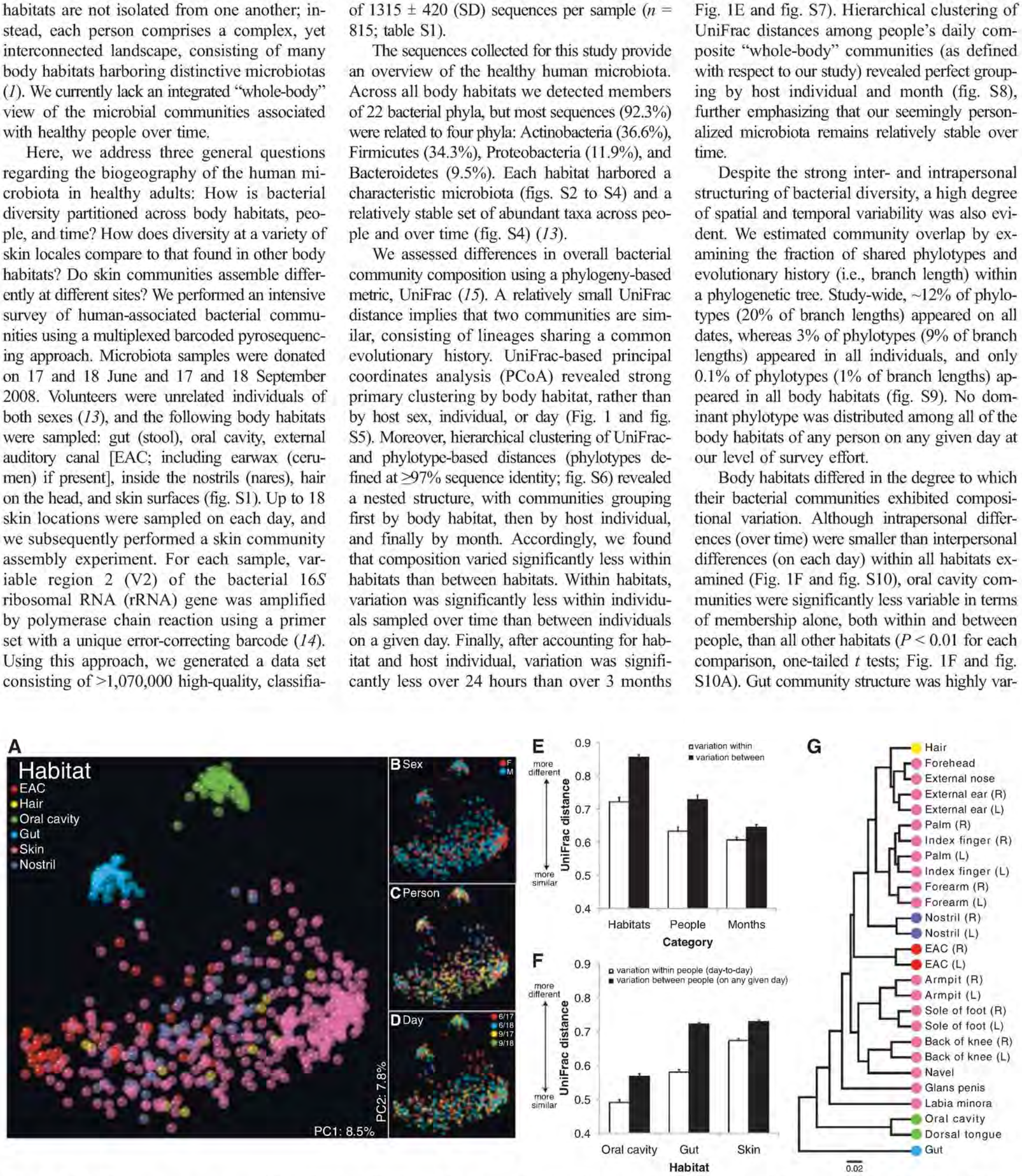

Fig. 1. 16*S* rRNA gene surveys reveal hierarchical partitioning of human-associated bacterial diversity. (**A** to **D**) Communities clustered using PCoA of the unweighted UniFrac distance matrix. Each point corresponds to a sample colored by (A) body habitat, (B) host sex, (C) host individual, or (D) collection date. The same plot is shown in each panel. The percentage of variation explained by the plotted principal coordinates is indicated on the axes. F, female; M, male. (**E** and **F**) Mean (±SEM) unweighted UniFrac distance between communities. In (E) habitats are weighted equally, and in (F) skin comparisons are within sites. (**G**) Hierarchical clustering of composite communities from the indicated locales. Leaves are colored according to body habitat as in (A). The bar represents a weighted UniFrac distance of 0.02. R, right; L, left.

iable among people, but exhibited minimal variability within people over time (Fig. 1F and fig. S10). Skin (within sites), hair, nostril, and EAC communities had the highest levels of intrapersonal variability in membership over time and were roughly on par with the gut in terms of interpersonal variability (Fig. 1F and fig. S10A). These results indicate that the size of the community "core" (the set of phylotypes shared among all individuals) will depend on the body habitat examined and is likely to be larger in the oral cavity than in other habitats such as the gut or skin.

Compositional variation in skin bacterial communities was also attributable to differences among sites within hosts: The average site-to-site UniFrac distance within people was higher than the inter- and intrapersonal variability observed within sites. To gain insight into the shared community structure of skin sites in relation to one another and other body habitats, we performed hierarchical clustering of weighted UniFrac distances, which account for relative abundances as well as membership (*16*) (Fig. 1G and fig. S11). We found that right and left sides of the body grouped together with the exception of index fingers, which clustered with their respective palms. Clustering revealed a "head" group, including the forehead, external nose, external ears (pinnae), and hair, dominated by Propionibacterineae (60 to 80%; fig. S12); and an "arm" group, including volar aspect of forearms, palms, and index fingers, where Propionibacterineae were less abundant (20 to 40%; fig. S12). Sites on the trunk and legs clustered separately and were dominated by *Staphylococcus* spp. [armpits (axillae) and soles of feet] or *Corynebacterium* spp. [navel (umbilicus) and backs of knees (popliteal fossae)] (fig. S12). It is proposed that site-to-site clustering of skin bacterial communities is driven by differences in skin environmental characteristics (*10*). Although the nostrils (nares) and EACs clustered with skin, they also harbored upper-respiratory commensals (e.g., *Branhamella* spp.) and taxa likely derived from earwax, respectively (fig. S4). The labia minora was divergent, as *Lactobacillus* spp., a common inhabitant of the female urogenital system, dominated this skin site (fig. S12). Finally, the oral cavity (mouth rinse samples) and dorsal tongue, which clustered together, along with the gut were most divergent from skin and other communities. These patterns were also evident when we mapped the relative abundances of core (i.e., shared by all people in our study) and peripheral taxa found within the 27 communities onto the human body (fig. S13).

Skin sites vary markedly in their level of bacterial diversity (*10*) (fig. S14). Moreover, we found that high-diversity skin locations harbored as many phylotypes as or more phylotypes than the gut or oral cavity (fig. S15) and significantly more phylogenetic diversity (i.e., branch length; Fig. 2A) than the gut or oral cavity given our survey effort. Indeed, most people on most days had at least one, and often many skin sites harboring diversity as high as or higher than that of their gut. On average, high-diversity skin sites included the forearm, palm, index finger, back of the knee, and sole of the foot. Other sites (e.g., the forehead) had lower diversity (fig. S14). Skin sites were also compositionally distinct (fig. S16), as highlighted by PCoA of UniFrac distances between forehead (low-diversity) and forearm (high-diversity) communities (Fig. 2B). Notably, site-to-site differences in skin diversity were inter- and intrapersonally robust: Forehead diversity was lower than palm diversity in each person on each day (Fig. 2C), and this was also true for forehead versus forearm communities (fig. S17).

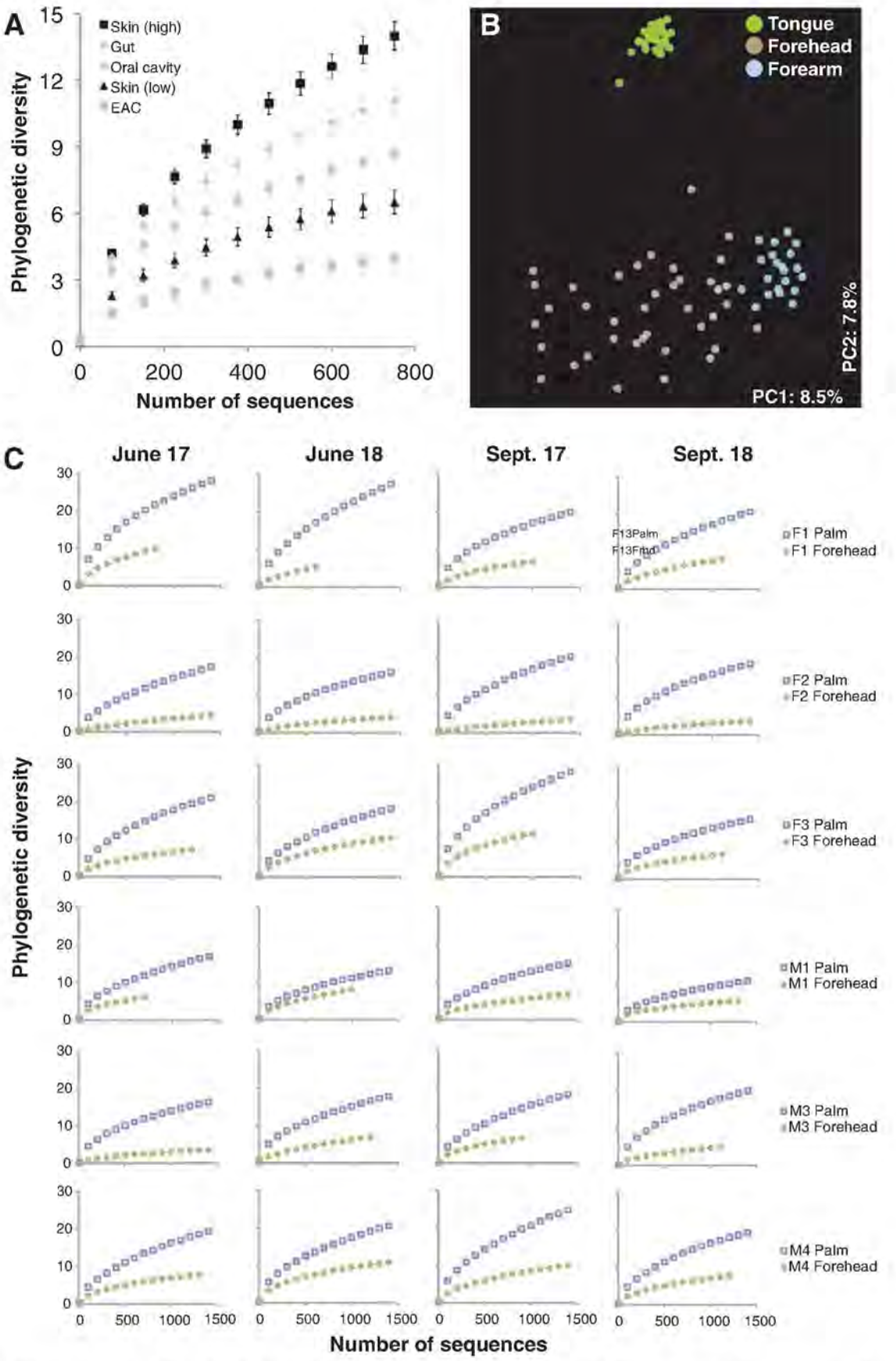

Fig. 2. Site-to-site variation on skin surfaces. **(A)** Rarefaction curves for communities sampled from skin and other habitats. Phylogenetic diversity is in units of branch length. Mean ± 95% confidence interval shown. **(B)** PCoA plot as in Fig. 1 showing only dorsal tongue, forehead, and volar forearm samples. The percentage of variation explained by the plotted principal coordinates is indicated on the axes. **(C)** Individual rarefaction curves for forehead and palm communities.

These and others' results (*10*) indicate that skin bacterial communities exhibit predictable biogeographic patterns. However, it is unclear whether these patterns arise because of differences in current environmental factors (e.g., local chemistry, nutrient availability), historical exposures (i.e., microbes available to colonize), or both (*17*, *18*). To address this question, and to gain insight into the community assembly patterns of skin bacterial communities, we carried out an experiment in which plots on the foreheads and left volar forearms of volunteers were

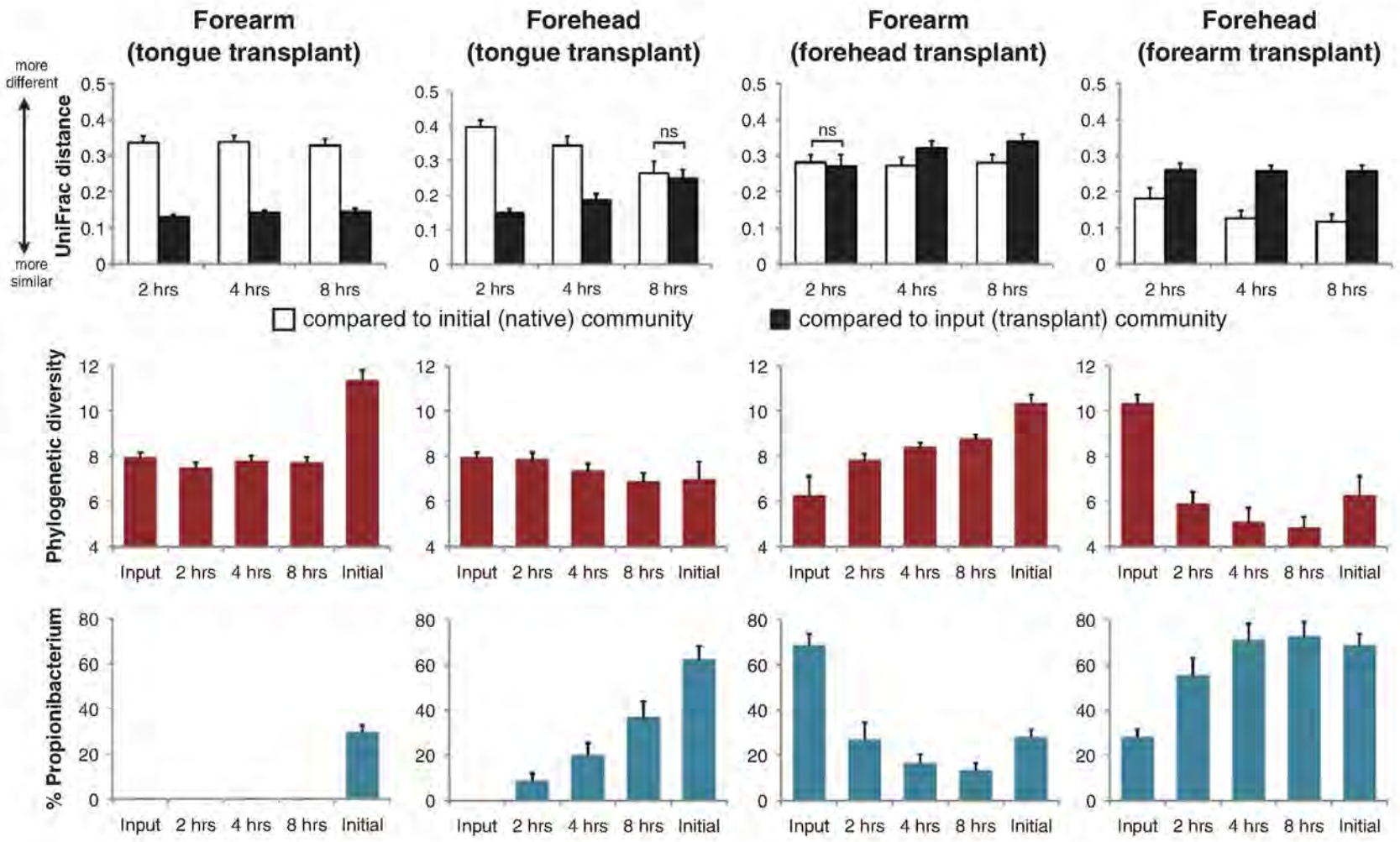

Fig. 3. Community assembly on forehead versus volar forearm skin surfaces. (**Upper**) Mean (±SEM) weighted UniFrac distance between communities. At each time point, $P < 0.01$ unless indicated; two-tailed t tests. ns, not significant. (**Middle**) Mean (±SEM) phylogenetic diversity controlled for sampling effort. (**Bottom**) Mean (±SEM) relative abundance of *Propionibacterium* spp.

disinfected, inoculated with foreign microbiotas (i.e., defined historical exposures), and tracked over time (*13*) (fig. S18).

Skin bacterial community assembly proceeded differently on the forehead than on the volar forearm. At 2, 4, and 8 hours after transplant, forearm plots (n = 16) inoculated with tongue bacteria were more similar to tongue communities than to native forearm communities in composition, diversity, and the relative abundance of *Propionibacterium* spp. (Fig. 3 and fig. S19). Conversely, forehead plots (n = 16) inoculated with tongue bacteria grew more similar to native forehead communities over time, as seen in overall structure and the relative abundance of *Propionibacterium* spp. (Fig. 3). Thus, on the forehead, factors additional to the history of exposure to tongue bacteria shaped community assembly. Forearm and forehead plots (n = 16 each) inoculated with each other's microbiota appeared to assemble communities that were more similar to their initial native microbiota than to the transplants (Fig. 3). Intrapersonal and same- and opposite-sex interpersonal transplants performed similarly (figs. S20 and S21). While acknowledging that our conclusions might change given a longer observation period, we suggest that environmental characteristics play a stronger role in shaping skin bacterial communities at sebaceous sites such as the forehead than at dry sites such as the forearm, either by selecting for the native microbiota, against the foreign microbiota, or by supporting more rapid growth and/or recolonization from sites protected from disturbance.

These findings have a variety of implications for the practice of medicine, both from the perspective of prevention and therapeutics. For example, they emphasize the need to (i) specify body habitat when conducting in-patient microbial surveillance studies designed to examine the flow of normal and pathogenic organisms into and out of different body sites in patients and their health care providers; (ii) determine the local biotic and abiotic conditions of subsites of a given body habitat such as the skin to understand why some subsites are more or less resistant to invasion; and (iii) designate those sites that are amenable to transplantation of microbial communities with natural or engineered metabolic capacities that would be beneficial to a host.

Our work also ties together two emerging themes from studies of human-associated microbial communities: high levels of variability among individuals in every body habitat studied to date, including the gut (*6*, *7*), skin (*8*–*10*), and oral cavity (*11*, *12*), and relative stability within individuals (*7*, *10*). These patterns suggest that the search for microbial factors associated with disease, although difficult to ascertain due to the high intrinsic levels of variability among healthy individuals, may be achievable using broad profiling techniques such as those employed here.

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Supporting Online Material

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Materials and Methods
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Figs. S1 to S22
Table S1
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The Fanconi Anemia Pathway Promotes Replication-Dependent DNA Interstrand Cross-Link Repair

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Fanconi anemia is a human cancer predisposition syndrome caused by mutations in 13 *Fanc* genes. The disorder is characterized by genomic instability and cellular hypersensitivity to chemicals that generate DNA interstrand cross-links (ICLs). A central event in the activation of the Fanconi anemia pathway is the mono-ubiquitylation of the FANCI-FANCD2 complex, but how this complex confers ICL resistance remains enigmatic. Using a cell-free system, we showed that FANCI-FANCD2 is required for replication-coupled ICL repair in S phase. Removal of FANCD2 from extracts inhibits both nucleolytic incisions near the ICL and translesion DNA synthesis past the lesion. Reversal of these defects requires ubiquitylated FANCI-FANCD2. Our results show that multiple steps of the essential S-phase ICL repair mechanism fail when the Fanconi anemia pathway is compromised.

Cells derived from Fanconi anemia (FA) patients are hypersensitive to agents that induce DNA interstrand cross-links (ICLs) and exhibit ICL-induced chromosomal instability (*1*, *2*). Eight FANC proteins form a nuclear "core complex," which mono-ubiquitylates the FANCI-FANCD2 complex after DNA damage (*3*–*5*). Ubiquitylated FANCI-FANCD2 is recruited to the chromatin where it colocalizes with DNA repair factors (*6*, *7*). Mutation of the ubiquitin acceptor site in FANCD2 prevents FANCI-FANCD2 chromatin binding and sensitizes cells to ICL-inducing agents (*4*). Although the FA pathway might play a minor role in ICL repair during G_1 phase (*8*, *9*), its primary function is exerted in S phase (*6*, *10*–*13*). These results suggest that ubiquitylated FANCI-FANCD2 controls ICL repair in S phase, but the underlying mechanism is unknown.

Xenopus egg extracts support replication-dependent repair of a plasmid containing a cisplatin ICL (pICL) (*12*) (fig. S1A). Initially, two replication forks converge on the ICL, with their leading strands stalling 20 to 40 nucleotides (nt) from the lesion (Fig. 1A, i). One of the two leading strands then approaches the ICL, stalling again 1 nt from the cross-linked base [the "–1" position (Fig. 1A, ii)]. Subsequently, incisions on the other parental strand uncouple the cross-link (Fig. 1A, ii, green scissors), and lesion bypass occurs in two steps. First, a nucleotide is inserted across from the damaged template base ["insertion" (Fig. 1A, iii)], after which the strand is extended beyond the ICL in a DNA polymerase ζ–dependent manner ["extension" (Fig. 1A, iv)]. The final steps in repair are thought to involve excision repair and/or homologous recombination (Fig. 1A, v).

To examine the function of the *Xenopus laevis* FANCI-FANCD2 complex in ICL repair, we coexpressed xlFANCI (fig. S2) and xlFANCD2 (*10*, *14*) in insect cells and purified a stable 1:1 FANCI-FANCD2 complex (Fig. 1B and fig. S3A). Using antibodies to FANCI (fig. S3B) and

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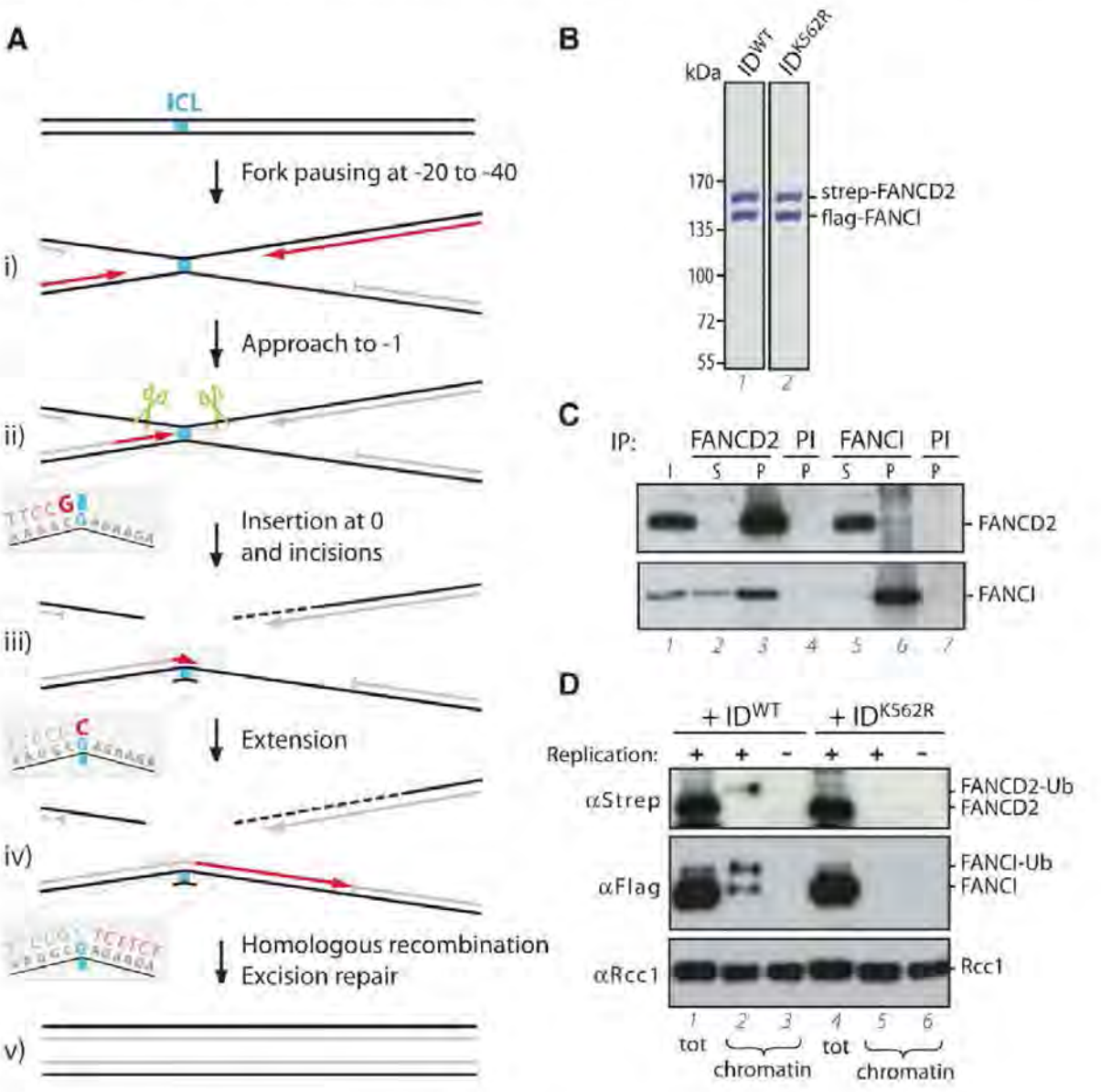

Fig. 1. (**A**) Schematic representation of lesion bypass in ICL repair (*12*). (**B**) Purified FANCI-FANCD2^{WT} and FANCI-FANCD2^{K562R} stained with Coomassie blue. (**C**) Reciprocal co-immunoprecipitation of xlFANCI and xlFANCD2 from *Xenopus* egg extract. Input (I) and supernatant (S) (0.2 μl extract), or precipitated proteins (P, from 1 μl extract) were blotted for FANCI and FANCD2. PI, preimmune serum. (**D**) Replication-dependent binding of FANCI-FANCD2 to damaged chromatin. Cross-linked sperm chromatin was replicated in extracts supplemented with FANCI-FANCD2^{WT} or FANCI-FANCD2^{K562R} (310 nM). Chromatin-bound fractions (from 2 μl extract) or total extract (0.2 μl), were analyzed by Western blotting with antibodies against a strep tag (recombinant FANCD2), a FLAG tag (recombinant FANCI), and RCC1 (loading control). Where indicated, replication was inhibited with Geminin. Note that only ubiquitylated FANCD2 binds chromatin, whereas both ubiquitylated and unubiquitylated FANCI bind [see also (*16*)].

FANCD2 (*12*), we showed that, in *Xenopus* egg extracts, FANCI and FANCD2 interact (Fig. 1C) and that the proteins undergo replication-dependent mono-ubiquitylation and chromatin binding, both of which are greatly enhanced by the presence of an ICL (fig. S3, C to E) (*10*). We also purified FANCI-FANCD2^{K562R}, in which the ubiquitin acceptor lysine at position 562 in FANCD2 is replaced by an arginine (Fig. 1B). Unlike FANCI-FANCD2^{WT}, FANCI-FANCD2^{K562R} did not bind to chromatin (Fig. 1D, compare lanes 2 and 5). In summary, *Xenopus* FANCI-FANCD2 binds chromatin dependent on DNA damage, FANCD2 ubiquitylation, and DNA replication.

To investigate whether FANCD2 is required for ICL repair, >95% of FANCD2 was immunodepleted from *Xenopus* egg extracts, resulting in ~75% codepletion of FANCI (fig. S4A), but no significant defect in total DNA synthesis on pICL (fig. S4B). Repair efficiency was determined by measuring the regeneration of a Sap I restriction

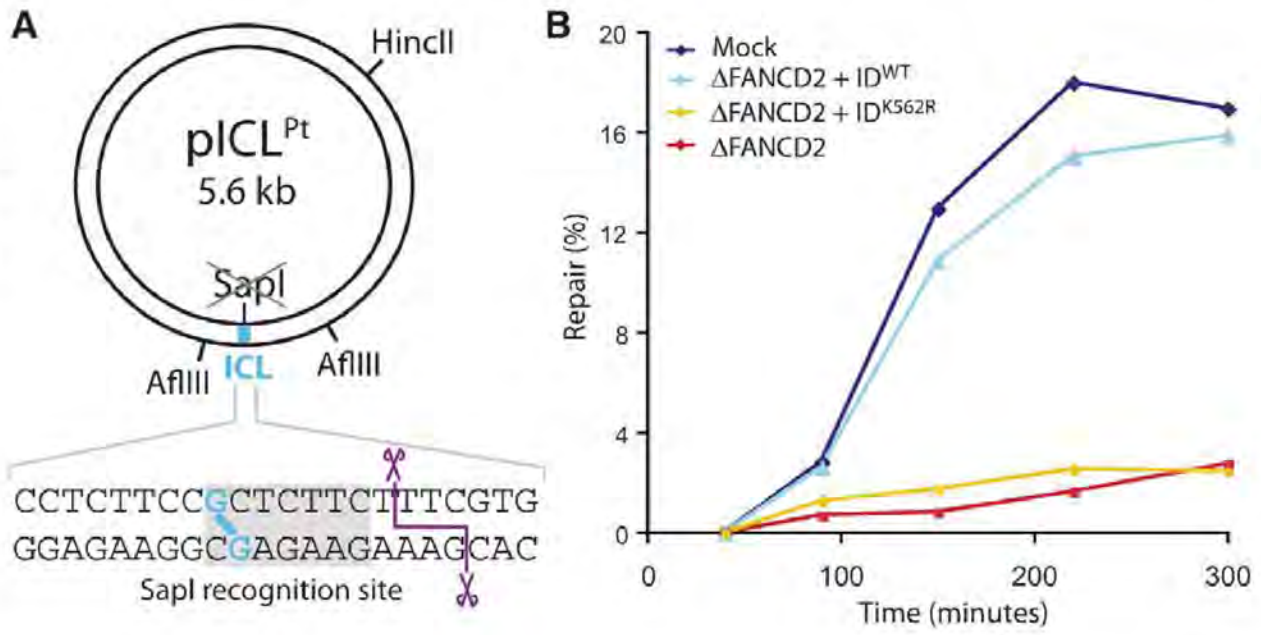

Fig. 2. FANCD2 and its ubiquitylation are required for ICL repair. (**A**) Sequence surrounding the ICL and relevant restriction sites of pICL. (**B**) pICL (2.3 ng/μl) was replicated in the presence of [α-^{32}P]deoxyadenosine triphosphate in mock-depleted extract, FANCD2-depleted extract (ΔFANCD2), or ΔFANCD2 extract supplemented with 375 nM FANCI-FANCD2^{WT} or FANCI-FANCD2^{K562R}, and repair efficiency was plotted. For primary data and calculation of repair efficiency, see fig. S5.

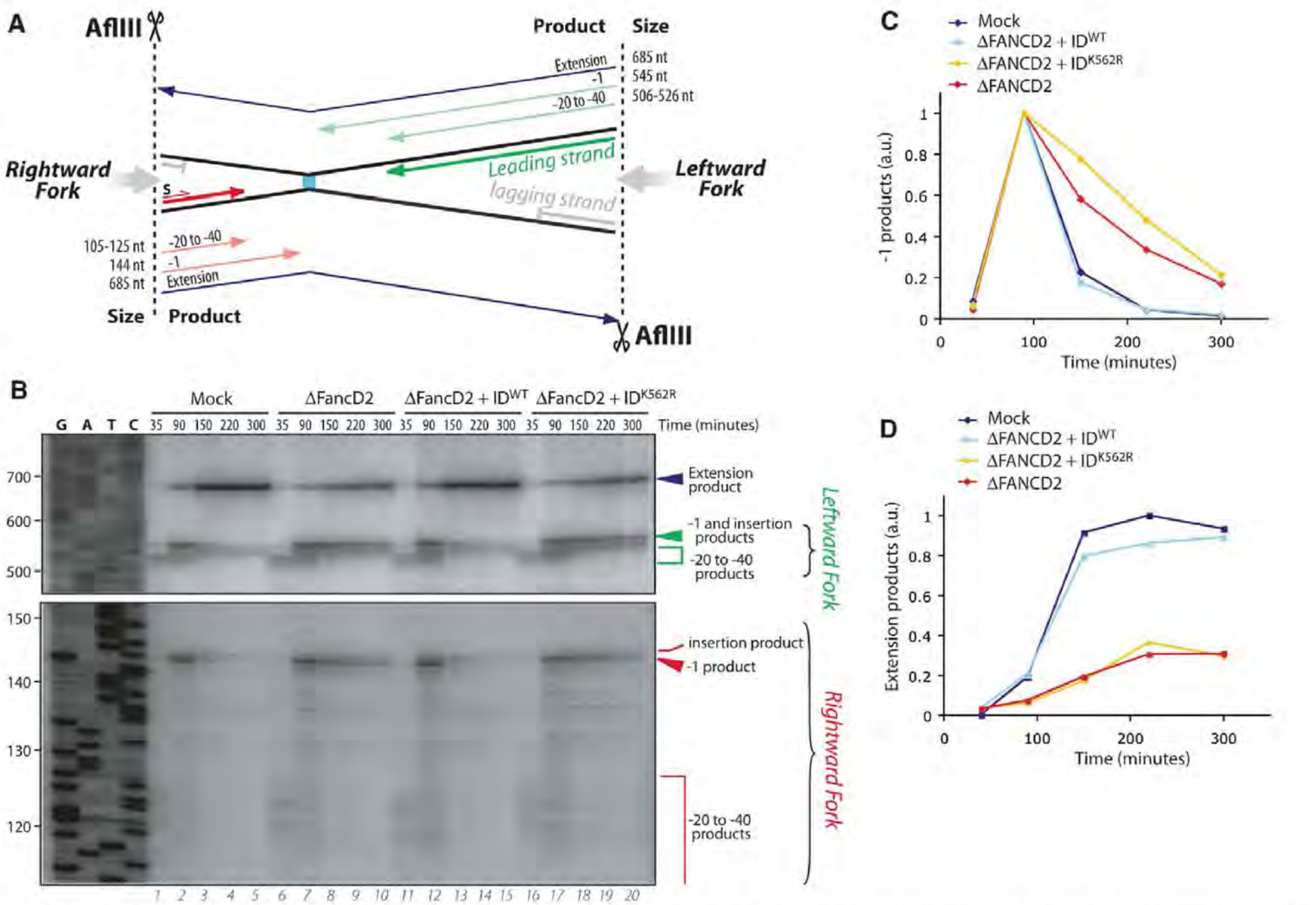

Fig. 3. Insertion of a nucleotide across from the damaged base is compromised in FANCI-FANCD2–deficient extracts. (**A**) Schematic representation of leading strand intermediates generated after pICL digestion with Afl III. (**B**) Samples from the reactions described in Fig. 2B were digested with Afl III, separated on a sequencing gel alongside a ladder derived from extension of primer S [S in (A)] on pControl, and visualized via autoradiography. Nascent strands generated by the rightward (red) and leftward (green) replication forks are indicated to the right and illustrated in (A). The −1 and extension products observed in (B) were quantified and graphed in (**C**) and (**D**), respectively.

site that coincides with the cross-link (Fig. 2A and fig. S5). In mock-depleted extracts, 15 to 24% of the replicated DNA became cleavable by Sap I (Fig. 2B and fig. S6). Sap I site regeneration is not 100% efficient because of significant destruction of the incised sister chromatid (*12*), incomplete removal of the unhooked ICL (*12*), and possibly some mutagenic lesion bypass events. In FANCD2-depleted extracts, regeneration of the Sap I site was reduced by a factor of 14, on average (Fig. 2B and fig. S6). The residual Sap I cleavable products might arise from incomplete FANCD2 depletion or FANCD2-independent ICL repair. Addition of recombinant FANCI-FANCD2 (Fig. 1B) rescued the repair defect (Fig. 2B and fig. S6), which ruled out the possibility that FANCD2 depletion nonspecifically inactivated repair. In contrast, FANCI-FANCD2^{K562R}, which is not ubiquitylated (fig. S4C), did not rescue repair (Fig. 2B and fig. S6), which demonstrated a role for ubiquitylated FANCI-FANCD2 in replication-coupled ICL repair. A recent study concluded that FANCL depletion reduces origin-dependent ICL repair in *Xenopus* egg extracts, but the defect was minor (30%) and was not rescued with recombinant proteins (*8*). Our experiments demonstrate that the Fanconi anemia pathway is essential for replication-dependent ICL repair and, together with previous observations (*13*, *15*), provide powerful evidence that Fanconi anemia is a bona fide DNA repair disorder.

The ATR (ataxia telangiectasia mutated and Rad3-related) signaling pathway confers ICL resistance in vertebrate cells (*2*, *16*), and replication of pICL in *Xenopus* egg extracts activates ATR as measured by Chk1 and Rad1 phosphorylation (*12*) (figs. S1B and S7). However, the repair defects we observed in FANCD2-depleted extracts were not due to defective checkpoint activation (fig. S7).

To address which step in ICL repair is dependent on FANCI-FANCD2, we replicated pICL in mock-depleted or FANCD2-depleted extract and examined lesion bypass. To this end, DNA samples were withdrawn at various times; digested with Afl III, which cuts on either side of the ICL (Fig. 3A); and nascent products were analyzed on a sequencing gel. In mock-depleted extract, the leading strands of the leftward and the rightward forks initially stalled 20 to 40 nt from the ICL (Fig. 3B, lane 1, green and red brackets), as previously described (*12*) (Fig. 1A). Then, one of the two forks resumed synthesis and stalled again 1 nt before the cross-linked base, causing a peak of "–1" products at ~90 min (Fig. 3B, lane 2, green and red arrowheads). Finally, insertion of a nucleotide across from the adducted base followed by extension resulted in formation of a 685-nt extension product (Fig. 3B, lanes 3 to 5, blue arrowhead). In FANCD2-depleted extracts, there was a marked persistence of the –1 product and a reduction in extension products, indicating an insertion defect (Fig. 3B, lanes 6 to 10; for quantification, see Fig. 3, C and D, and fig. S8). Extension products continued to accumulate slowly in the absence of FANCI-FANCD2 (Fig. 3D and fig. S8), but this was not accompanied by a proportional increase in repair products (Fig. 2B and fig. S6), suggestive of a FANCD2-independent, error-prone lesion-bypass process. The defects observed in FANCD2-depleted extracts were fully rescued by recombinant FANCI-FANCD2^{WT} but not by FANCI-FANCD2^{K562R} (Fig. 3, B to D, and fig. S8). In the samples lack-

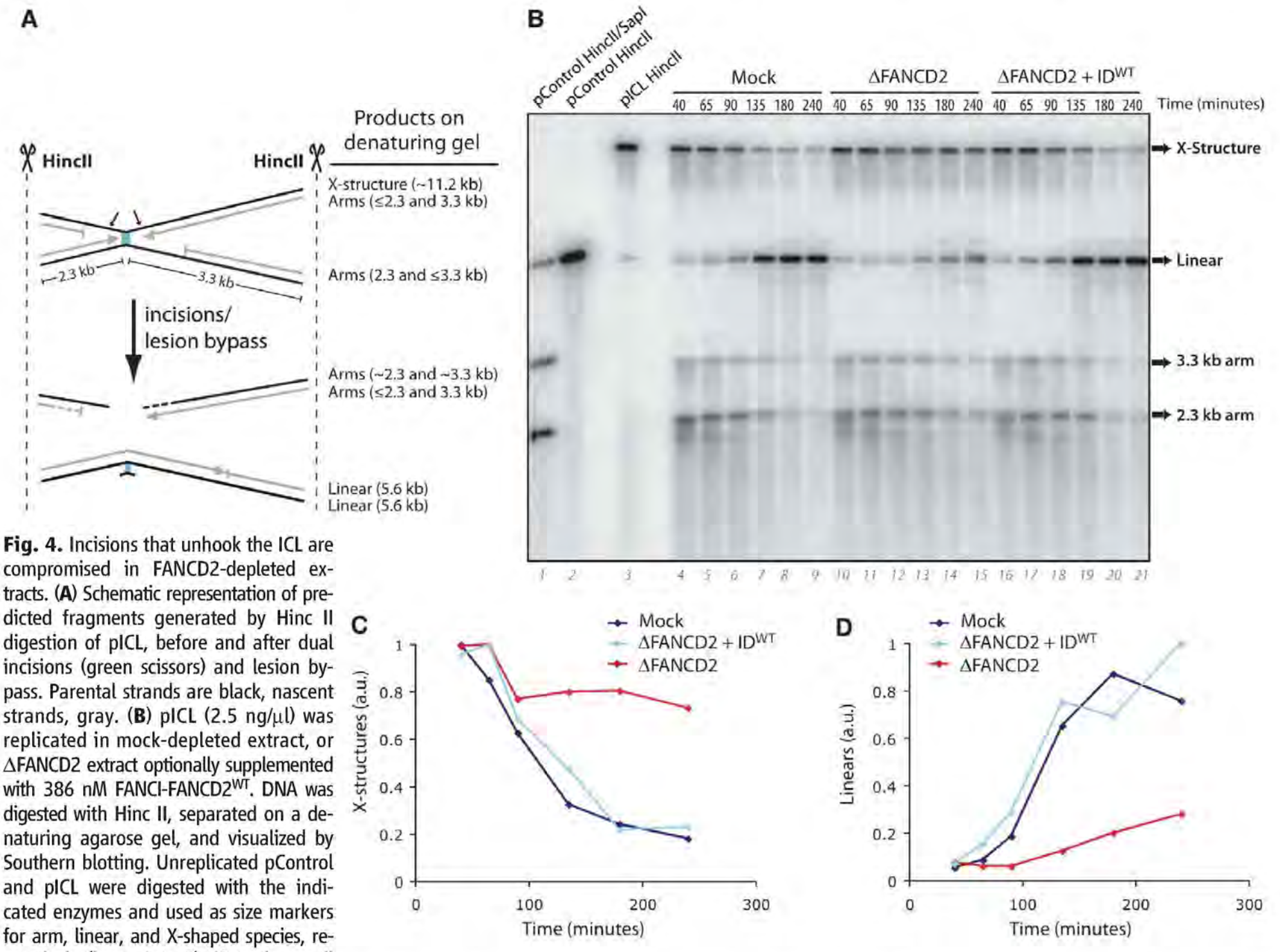

Fig. 4. Incisions that unhook the ICL are compromised in FANCD2-depleted extracts. (**A**) Schematic representation of predicted fragments generated by Hinc II digestion of pICL, before and after dual incisions (green scissors) and lesion bypass. Parental strands are black, nascent strands, gray. (**B**) pICL (2.5 ng/μl) was replicated in mock-depleted extract, or ΔFANCD2 extract optionally supplemented with 386 nM FANCI-FANCD2^{WT}. DNA was digested with Hinc II, separated on a denaturing agarose gel, and visualized by Southern blotting. Unreplicated pControl and pICL were digested with the indicated enzymes and used as size markers for arm, linear, and X-shaped species, respectively (lanes 1 to 3). Note the small amount of linear products in lane 3 (3% of the total), which represents contaminating non–cross-linked plasmids. X-shaped structures and linear species observed in (B) were quantified and graphed in (**C**) and (**D**), respectively.

ing functional FANCI-FANCD2, the level of –1 products did eventually decrease (Fig. 3, B and C, and fig. S8). However, since the extension products never accumulated to more than ~30% of the mock-depleted samples (Fig. 3D and fig. S8), we infer that this decline of –1 products is primarily due to degradation (*12*). We conclude that in the absence of FANCI-FANCD2, nucleotide insertion opposite the cross-linked base is inhibited. This differs from the effect of DNA polymerase ζ immunodepletion, which arrests lesion bypass immediately after the insertion step (fig. S9) (*12*).

We next investigated whether FANCI-FANCD2 is required for incisions, which are thought to occur on one of the parental strands on either side of the lesion (*2*) (Fig. 1A, ii). To visualize incisions, DNA repair intermediates were digested with Hinc II and analyzed by denaturing gel electrophoresis and Southern blotting (Fig. 4A). After 40 min, the most abundant species were the high-molecular-weight parental X-shaped molecules, as well as 2.3- and 3.3-kb species that represent stalled nascent strands (Fig. 4B, lane 4). Dual incisions surrounding the ICL are expected to convert the parental X-shaped molecule into a 5.6-kb linear product and 2.3- and 3.3-kb fragments (Fig. 4A). As expected, in mock-depleted extract, we observed a time-dependent decrease of X-shaped molecules and a concomitant increase in linear species (Fig. 4B, lanes 4 to 9; quantified in Fig. 4, C and D). The 2.3- and 3.3-kb species declined over time because of lesion bypass and/or resection (Fig. 4B). The kinetics of X-shaped molecule disappearance in this assay confirmed our previous conclusion (*12*) that the majority of incisions occurs after forks reach the –1 position (fig. S10C).

In the absence of FANCD2, incisions were severely inhibited, as seen from the persistence of X-shaped species and a severe delay in the accumulation of linear molecules (Fig. 4B, lanes 10 to 15; quantified in Fig. 4, C and D). In addition, the 2.3- and 3.3-kb fragments persisted longer, likely because of inhibition of lesion bypass. These effects were rescued by FANCI-FANCD2^{WT}. Tracking only the parental strands in this assay confirmed that incisions are inhibited in the absence of FANCD2 and showed that the defect is not rescued by FANCI-FANCD2^{K562R} (fig. S11). Together, these data show that ubiquitylated FANCI-FANCD2 is required for efficient incisions surrounding the cross-link.

Finally, we examined the precise timing of FANCI-FANCD2 ubiquitylation. As shown in fig. S12C, FANCI and FANCD2 ubiquitylation correlated with the arrival of leading strands at the –1 position, consistent with a role for the FANCI-FANCD2 complex in the insertion and incision steps, which occur after forks reach the –1 position (*12*) (figs. S10 and S12).

Using a chemically homogeneous cisplatin ICL and a bona fide repair assay, we show that the Fanconi anemia pathway is required for DNA replication–coupled ICL repair. These results explain why Fanconi anemia cells treated with ICL-inducing agents arrest late in S phase (*11*) and eventually die. We further demonstrate that FANCI-FANCD2 must be ubiquitylated to support repair, which suggests that its role in this process involves direct binding to the lesion. In the absence of FANCI-FANCD2, incisions near the ICL and translesion synthesis (TLS) past the lesion are severely inhibited, defining two critical steps in ICL repair that fail when the Fanconi anemia pathway is compromised. Although at present we cannot determine whether the insertion or incision steps occur first, it is widely envisioned that incisions must precede insertion (*2*). In this view, FANCI-FANCD2 might directly promote incisions and thereby affect TLS indirectly (fig. S13A). For example, FANCI-FANCD2, which contains no apparent nuclease domains, could promote dual incisions by recruiting the Slx4 nuclease complex to the lesion (*17*). However, we cannot rule out the converse scenario, in which TLS precedes incisions (fig. S13B), which would involve translesion DNA synthesis past an ICL (*18*). In this case, the primary function of FANCI-FANCD2 might be to promote TLS, perhaps via interaction with the ubiquitin-binding domains of Rev1. This model is consistent with genetic epistasis between TLS polymerases and the FA pathway (*19*), as well as reduced damage-dependent mutagenesis in FA cells (*20*). Finally, FANCI-FANCD2 might directly control both the incision and insertion steps (fig. S13C). Future experiments will be required to establish a molecular model of how FANCI-FANCD2 regulates the incision and/or TLS machineries during replication-coupled ICL repair.

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Indirect Punishment and Generosity Toward Strangers

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Many people incur costs to reward strangers who have been kind to others. Theoretical and experimental evidence suggests that such "indirect rewarding" sustains cooperation between unrelated humans. Its emergence is surprising, because rewarders incur costs but receive no immediate benefits. It can prevail in the long run only if rewarders earn higher payoffs than "defectors" who ignore strangers' kindness. We provide experimental evidence regarding the payoffs received by individuals who employ these and other strategies, such as "indirect punishment" by imposing costs on unkind strangers. We find that if unkind strangers cannot be punished, defection earns most. If they can be punished, however, then indirect rewarding earns most. Indirect punishment plays this important role, even if it gives a low payoff and is rarely implemented.

Indirect reciprocity is widespread in human societies. It occurs when we incur costs to reward those we know have been kind to others or punish those we know have been unkind to others. Indirect reciprocity is based on reputation and helps to enforce trustworthy behavior between individuals who do not know each other and who may not meet again. Such encounters form a substantial part of our interactions and are especially frequent in online commerce.

Indirect reciprocity is at work, for example, when someone financially supports anonymous volunteers working at food banks that help the poor, even though this person does not face the risk of ever needing a food bank's services. The donor's helping behavior is, therefore, called indirect rewarding. Such costly indirect rewarding is thought to be a key factor in the evolution of human cooperation (*1*–*4*). Experimental research (*5*–*8*) and theoretical considerations (*9*–*11*) suggest that indirect rewarding can sustain cooperation among unrelated humans. However, there is little empirical evidence about the long-term performance of indirect rewarding itself. People who engage in costly rewarding may lose out in the long run against "defectors" who never reward and thus avoid the associated costs. Even if good reputation is rewarded (*12*), indirect rewarders might lose out against "cautious defectors" who are generous only to avoid a bad reputation.

Indirect reciprocity may also take the form of costly indirect punishment. Though punishment has been observed to be important for promoting cooperative behavior in direct encounters (*13*), recent theoretical work suggests that it may be only marginally relevant when interaction is indirect (*14*). Empirical evidence on the use of indirect punishment and its long-term performance is missing, however.

We provide experimental evidence of human behavior in an anonymous environment where individuals can indirectly reward and punish. We determine the occurrences of different types of behaviors, including indirect rewarding, indirect punishment, defection, and cautious defection, among human participants and determine their payoff performance.

Our experimental design builds on the so-called "indirect helping game" (*5*, *8*, *9*). In total, 140 participants are repeatedly (100 rounds), anonymously, and randomly matched into donor-recipient pairs. Because roles are determined randomly, participants will typically be the donor in approximately half of the rounds. In the indirect helping game, only donors make decisions. In any round, each donor first observes the recipient's recent behavior in the role of donor and then decides whether to "help" the recipient or to "pass." Helping is costly for the donor and beneficial for the recipient, with the benefits exceeding the costs. In earlier experiments, indirect punishment was not available as an option, a restriction that is arguably not a realistic feature of human interactions (*13*–*16*). In our experiment, the donor can choose to "hurt" the recipient instead of passing or helping. Hurting is costly for the donor, but we vary its impact on the receiver. We conducted two treatments that differ only in this impact, which allows us to isolate the effect of indirect punishment on the payoff performance of different types of behavior. In our main treatment [harmful punishment (HP)], a hurt recipient loses 250 units of our experimental money, "francs." In the control treatment [symbolic punishment (SP)], a hurt recipient loses or earns no francs. We say that punishment is harmful in HP but only symbolic in SP. In both treatments, the donor loses 50 francs for hurting or 200 francs for helping, and the recipient earns 250 francs when he or she receives help. Passing does not affect either player's payoff. In both treatments the recipient observes the donor's action. Treatment SP is a control for HP, because it identifies differences in behavior between environments where indirect punishment has material consequences for the recipient and where it does not, while holding all other parameters constant across treatments (*17*–*19*).

Before choosing an action, donors observe a part of their recipient's donating history. A donor always learns his or her recipient's three most recent actions (first-order information) and, for a small price, can access the first-order information their recipients observed when making these decisions (second-order information). For treatments HP and SP, we collected data for, respectively, 8 and 6 independent cohorts of 10 participants.

The aggregate frequency (60.7%) of helping choices in our experiment falls within the range (50 to 85%) observed in experiments without the option of indirect punishment (*5*, *8*). Comparing HP to SP surprisingly shows that, in spite of the possibility of imposing costs on uncooperative recipients in HP, the two treatments exhibit no significant differences in average helping rates. Donors choose help with 60.0% frequency, on average, across the six cohorts in SP and 61.2% frequency, on average, across the eight cohorts in HP. This difference is not significant ($z = -0.065$, $P = 0.95$, two-sided Mann-Whitney U test, $N =$ 14 cohorts). Because behavior in both treatments displays a pronounced endgame effect, we restrict our analysis to the first 90 rounds (*17*).

In SP, punishment is very rare (1.1%), which is not surprising because it is costly for the donor but only symbolic to the recipient. When punishment is harmful (HP), it is used significantly more often ($z = -2.207$, $P = 0.027$, two-sided Mann-Whitney U test, $N = 14$) but still infrequently (3.4%). In both treatments, donors typically reward kind behavior with helping. When the recipient's history reveals unkind behavior toward others, donors more often pass than hurt. This preference for passing may explain why the punishment option in HP fails to increase cooperation beyond levels obtained without an option to punish (*5*, *8*). The infrequent use of punishment in our indirect reciprocity game seems to contrast the experimental results from public goods games with direct punishment, where frequent punishment of defectors sustains cooperation in the short (*13*, *20*) and intermediate run (*21*). This difference in results might be driven by the structural differences between the games. In our indirect reciprocity game, each action is indirect and targeted at a single person. In contrast, only punishment can be targeted at a specific person in public goods games, whereas any other action affects every member of the group. In combination with the difference in parameters, this may explain the level of punishment we observe (*17*).

Recent evidence suggests that human reciprocity is driven to a large extent by stable behavioral strategies (*22*–*24*), and a rich set of such strategies has been identified in recent models of evolution of indirect reciprocity (*1*, *9*, *10*). We consider seven prominent behavioral strategies and assess their payoff performance. These strategies are partitioned along the different ways a donor may use his or her own history or that of the recipient when choosing an action (*10*).

The first partition distinguishes between "discriminate" and "indiscriminate" strategies. An indiscriminate strategy does not condition an action on the donor's or recipient's histories. For example, "indiscriminate altruism" always prescribes help, and "indiscriminate defection" always prescribes pass.

The second partition divides discriminate strategies into those with selfish concern ("self-regarding") and those with concern for others ("other-regarding"). The strategy "cautious defection" employs occasional helping to maintain the donor's good reputation. In particular, it prescribes to help only when the donor's own

Table 1. Strategies in the indirect reciprocity game with punishment. The percentages of individuals identified with a strategy are given in parentheses, with their percentage in SP shown first and their percentage in HP shown second.

	Self-regarding	Other-regarding			
Indiscriminate	Defectors (9.6%, 10.5%)	Altruists (7.7%, 9.2%)			
Discriminate	Cautious defectors (7.7%, 10.5%)	Rewarders		Punishers	
		Image (50.0%, 39.5%)	Standing (25.0%, 17.1%)	Image (0%, 5.3%)	Standing (0%, 7.9%)

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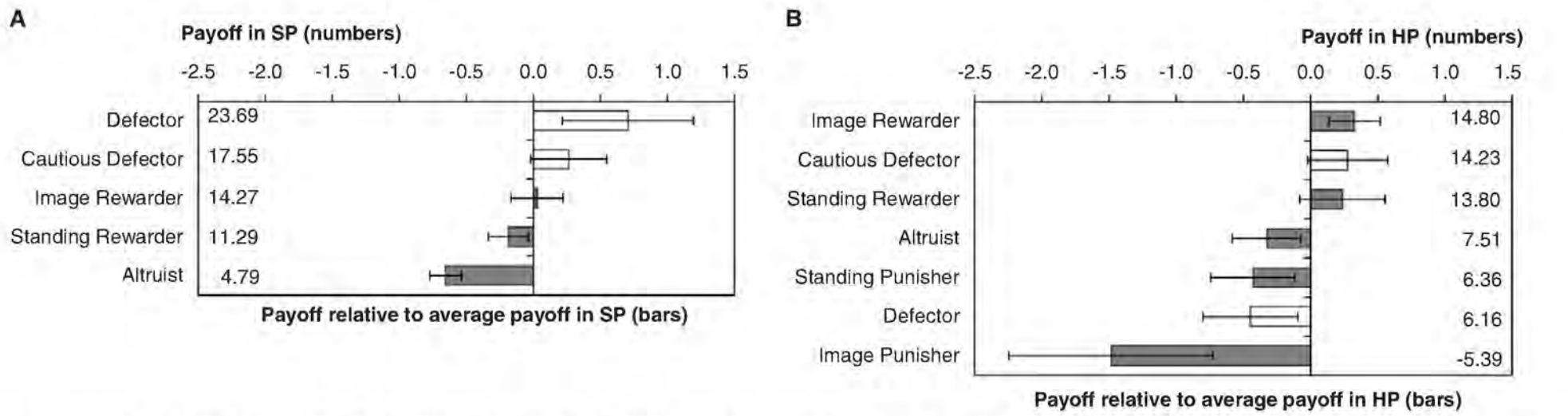

Fig. 1. Average and relative payoffs of the different strategies in SP (**A**) and in HP (**B**). Numbers inside the graph indicate average payoffs per round (in francs) of different strategies. Bars indicate the average payoffs of different strategies relative to the average payoffs across all participants in the respective treatment, and error bars indicate ±1 SE of these average relative payoffs. Tables S1 to S3 in the SOM (*17*) provide detailed information of payoffs for each strategy, cohort, and individual.

history shows little helping. Thus, it is discriminating and self-regarding (*10*).

Strategies that do condition actions on the recipient's history are discriminate and other-regarding. We focus on the "reciprocal" strategies that prescribe help only to those recipients whose history reveals frequent helping. The third partition divides the reciprocal strategies between "punishing" strategies that use the possibility to hurt unhelpful recipients and the "rewarding" strategies that do not.

The fourth partition divides the reciprocal strategies on the basis of the type and amount of information they use. This allows us to distinguish between standing and image scoring (*1*, *9*, *10*, *25*). An individual's "image score" and "standing" are statistics that summarize his or her reputation (*9*, *10*). A person's image score decreases when he or she passes and increases when he or she helps, whereas a person's standing decreases only when he or she passes on a recipient with a good reputation. An image-scoring strategy prescribes helping only those recipients with a high image score (*9*), and a standing strategy prescribes helping only those with high standing (*10*). Specifically, a standing strategy prescribes that a donor base his or her action not only on the first-order information about the recipient but also on the underlying second-order information. The latter indicates what the recipient knew about his or her recipient when choosing past actions as a donor. Using the combination of the final two partitions, we distinguish between "image rewarding," "image punishing," "standing rewarding," and "standing punishing." Because of the availability of hurting and the limits on the observable history in our experiment, we consider approximated standing and image-scoring strategies.

For each participant, we determine whether his or her actions across rounds 1 to 90 are consistent with any single behavioral strategy. Details and a graphic depiction of our classification procedure are provided in the supporting online material (SOM) (*17*). We refer to classified participants as rewarder, punisher, etc. Table 1 summarizes the identified strategies and shows for each the proportion of participants using that particular strategy. Almost all participants (SP: 86.7%; HP: 95.0%) can be classified. More classified participants use image-scoring strategies than standing strategies; among them, there are more rewarders than punishers. The next-largest fractions are those of indiscriminate and cautious defectors, with approximately half of them being cautious. The smallest group is formed by indiscriminate altruists.

Little is known about the payoff consequences of using various strategies in indirect reciprocity games (*12*, *26*). Such information is important because a strategy can flourish in the long run only if it yields a higher benefit than the alternatives. We consider the identified strategies and calculate the average cohort payoff generated by each of them (Fig. 1). For each participant, we calculate, in francs, the average earnings as a donor plus average earnings as a recipient across rounds 1 to 90. The payoff for a strategy is calculated for each cohort where the strategy is observed, as the average payoff across the participants using this strategy. These payoffs per cohort are used in our statistical analysis; however, it is the relative fitness of a strategy that determines its long-term success. Figure 1, therefore, shows for each treatment the average payoff of each strategy relative to the treatment average payoff. This relative payoff is calculated as [(average payoff of all participants in treatment using a particular strategy) − (average treatment payoff)]/(average treatment payoff).

Figure 1 reveals important payoff differences between the two treatments. In treatment SP, the indiscriminate defectors fare best (average payoff = 23.69 francs). Compared with the combined classes of defectors (20.96), the combined rewarders (13.28) earn significantly less ($P = 0.044$, two-sided Wilcoxon signed-ranks test, $N = 5$ paired observations); the altruists fare worst, and not only when compared with the defectors (4.79). Hence, defection outperforms all other strategies. In treatment HP, the payoffs are markedly different. The cautious defectors (14.23), image rewarders (14.80), and standing rewarders (13.80) are more successful than the indiscriminate defectors (6.16). Even if we combine the two classes of defectors (10.20), the combined rewarders (14.50) earn significantly more ($P = 0.068$, two-sided Wilcoxon signed-ranks test, $N = 8$ paired observations). Noticeably, the punishment strategies, which are used only in HP, are among the least successful (6.4).

The stark difference in the ranking of earnings across the two treatments is caused mainly by the distinctly lower earnings of indiscriminate defectors in HP, as compared with SP ($z = 1.715$, $P = 0.086$, two-sided Mann-Whitney U test, $N = 9$). This is a direct consequence of harmful punishment. The slightly higher punishment rate in HP (3.4%) than in SP (1.1%) is almost entirely directed toward defectors (SP: 1.6%; HP: 12.8%) ($z = 1.976$, $P = 0.048$, two-sided Mann-Whitney U test, $N = 9$) and cautious defectors (SP: 1.2%; HP: 5.2%) ($z = 1.375$, $P = 0.169$, two-sided Mann-Whitney U test, $N = 8$). Hence, though harmful punishment is rare, it substantially reduces defectors' earnings and changes the ranking of earnings among strategies.

Our results regarding the effects of indirect punishment complement recent experimental research showing that costly direct punishment may disfavor individuals and groups in repeated direct interactions with strangers, at least in the short run (*27*–*29*). However, our earnings comparisons across treatments reveal that, in indirect reciprocity games, punishment does not need to be frequent to promote the relative success of reward strategies. Theoretical models of indirect punishment investigating its long-term effects on cooperation are just starting to emerge (*14*). Our study can aid the development of such models by showing that indirect punishment, although rare, can support human cooperation.

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On the Origin of Species by Natural and Sexual Selection

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Ecological speciation is considered an adaptive response to selection for local adaptation. However, besides suitable ecological conditions, the process requires assortative mating to protect the nascent species from homogenization by gene flow. By means of a simple model, we demonstrate that disruptive ecological selection favors the evolution of sexual preferences for ornaments that signal local adaptation. Such preferences induce assortative mating with respect to ecological characters and enhance the strength of disruptive selection. Natural and sexual selection thus work in concert to achieve local adaptation and reproductive isolation, even in the presence of substantial gene flow. The resulting speciation process ensues without the divergence of mating preferences, avoiding problems that have plagued previous models of speciation by sexual selection.

Even as we commemorate the 150th anniversary of Darwin's *On the Origin of Species* (*1*), discussion continues on whether speciation is adaptive (that is, driven by selection) and to what extent it is inhibited by gene flow (*2*–*7*). Ecological conditions can induce natural selection for local adaptation (*2*, *8*), but disruptive or diversifying selection is usually not sufficient for speciation if individuals can migrate between habitats. In such cases, a mating structure has to emerge that strongly reduces hybridization between ecologically specialized populations (*3*–*5*).

Sexual selection is likely to play a pivotal role in shaping such a mating structure during incipient speciation (*9*) and has been suggested to induce speciation by causing the divergence of mating preferences between two emerging species (*9*–*13*). Yet speciation due to diverging mating traits is controversial, because existing theoretical models can explain the divergence of mating preferences only under conditions that are rarely met in nature (*10*, *13*, *14*). Moreover, the models tend to rely on Fisherian sexual selection to generate reproductive isolation. Fisher's runaway process of sexual selection involves preferences for arbitrary ornaments that reflect nothing but attractiveness (*15*). The runaway process could thus potentially evolve in different directions, allowing the divergence of preferences during speciation. However, mating preferences are generally not arbitrary but act on ornaments that indicate genetic or phenotypic quality (*15*–*17*), providing choosy individuals with either direct benefits or good genes for their offspring (*15*, *18*–*20*). The adaptive directionality of mate choice based on such indicator traits makes it difficult to conceive how this process could lead to the divergence of preferences between two nascent species.

By means of the following scenario, we will demonstrate that the divergence of mating preferences is not required for sexual selection to contribute to speciation. We consider a patchy environment that imposes contrasting selection pressures on an ecological character like a food-exploitation strategy (Fig. 1). We assume that across all habitats, intermediate ecological strategies, on average, do worse than specialist strategies optimizing the use of one of the habitats. Accordingly, natural selection is stabilizing within habitats but disruptive at the level of the entire population.

Individual-based computer simulations [based on Levene's "soft-selection" model (*21*), also see supporting online material (SOM)] that implement this ecological scenario highlight the overpowering effect of gene flow (Fig. 2A). Although disruptive selection removes individuals with intermediate phenotypes from the population, such individuals are created anew every generation as a result of migration between the habitats and recombination between different specialist genotypes. This process prevents the population from splitting into two locally adapted species, unless disruptive selection is unusually strong.

Having observed that ecological disruptive selection per se is not sufficient to result in speciation, we next consider an ornament, such as a plumage characteristic, that is expressed in a condition-dependent manner (*15*, *22*, *23*). Individuals adapted to the local environment are likely to be in a better condition, allowing them to develop brighter plumage than individuals that are less well adapted (*24*). Thus, by virtue of its condition-dependent expression, the ornament functions as an indicator for the degree of local adaptation (*25*–*27*).

Assuming that the ornament is expressed in males and that females are the choosy sex, one would expect females to evolve a preference for elaborate ornamentation, thereby using the information on local adaptation revealed by the male's ornament (*26*). Simulations that allow for the evolution of a preference and condition-dependent ornamentation [following (*17*); also see SOM] confirm this expectation (Fig. 2C). Starting from a randomly mating population ($p = t = 0$ at generation 0), female choosiness (p) evolved along with a concurrent increase in the resources invested by males in their ornament (t) to signal their ecological performance. The evolutionary process is driven by sexual selection and fueled by rare mutations introducing variation in female choosiness and male ornamentation. In our model, mating with a locally adapted partner is beneficial to a

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female because it increases, on average, the probability that her offspring will have an optimal phenotype in one of the habitat types and, thus, the highest fitness when selection is disruptive. Such preference for a locally adapted partner is even more advantageous when offspring are more likely to end up in the same habitat as the parents (for example, when individuals are philopatric to some degree) or exert matching habitat choice on the basis of their ecological phenotype (*28*).

Once mate choice has evolved, sexual selection acts alongside disruptive ecological selection to disfavor intermediate ecological phenotypes. This strengthens assortative mating with respect to the ecological strategy, reducing the rate of interbreeding between specialists for different habitats. In the rare event that habitat specialists do interbreed, sexual selection effectively removes their sons from the mating pool, as hybrid males will be of poor quality in either habitat, produce less attractive ornaments, and fail to attract females. Thus, mate choice based on an indicator of local adaptation enhances reproductive isolation between habitat specialists and should therefore increase the likelihood of speciation. Indeed, the added effect of sexual selection allows the population to split into two locally adapted specialist types (Fig. 2, B and C), whereas natural selection alone merely supports the maintenance of a broad unimodal distribution of phenotypes (Fig. 2A). Replicate simulations show that the waiting time to speciation is variable, but in all cases, the population splits quickly and irreversibly after female choosiness has increased beyond a critical level (fig. S1). A calculation of the selection gradients on the mating characters (see SOM) reveals that these features result from a positive feedback between the effectiveness of sexual selection and ecological divergence. Selection for increased choosiness is initially weak, but as the ecological phenotype distribution changes from unimodal to bimodal, quality differences between the males become more pronounced, providing increased benefits to choosiness (fig. S2).

To further assess the contribution of sexual selection to the speciation process, we ran simulations with and without sexual selection, systematically varying the migration rate (m) and the

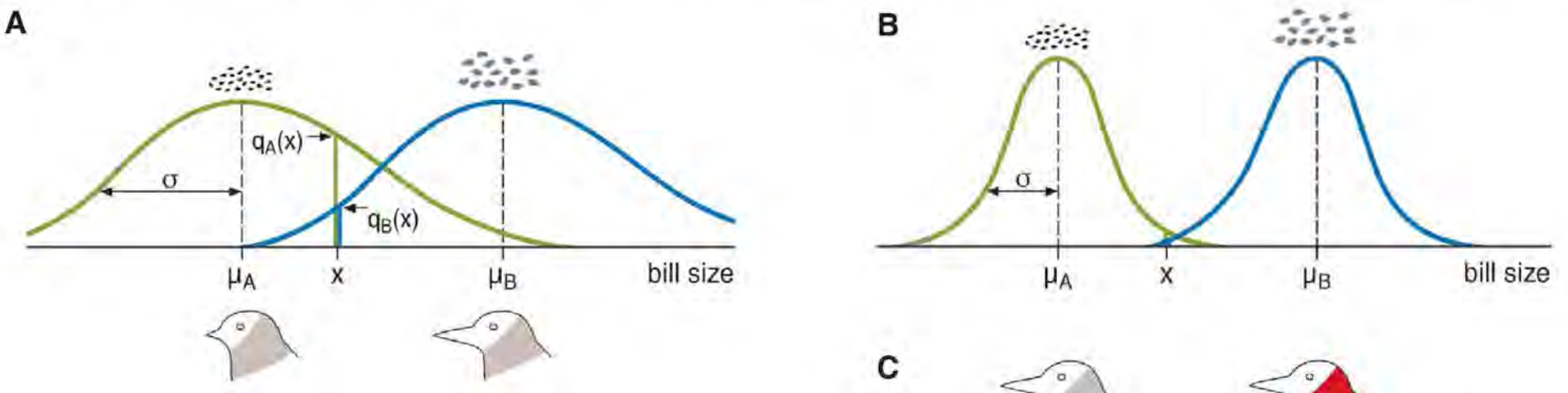

Fig. 1. Illustration of the model structure. Our model considers a patchy environment with differing environmental conditions (small seeds in patch A, large seeds in patch B). Organisms differ in an ecological character (bill size). The green Gaussian curve describes how fitness $q_A(x)$ in patch A varies with bill size x, whereas the blue curve characterizes fitness $q_B(x)$ in patch B. (**A**) In case of a wide fitness curve (large σ), a bird with an intermediate bill size x achieves a higher average fitness across habitats $\frac{1}{2}[q_A(x) + q_B(x)]$ than a small-seed specialist ($x = \mu_A$) or a large-seed specialist ($x = \mu_B$). Hence, selection is stabilizing and favors a generalist food-exploitation strategy (i.e., an intermediate bill size). (**B**) If σ is small, the fitness of the generalist strategy is very low. Selection is disruptive, favoring the two specialist food-exploitation strategies. (**C**) The colored collar represents a sexual ornament that is expressed in a condition-dependent manner. For the same allocation of resources to the ornament, small-billed birds can produce a more attractive (red) ornament in the small-seed patch A (labeled "habitat A" in the figure), whereas large-billed birds can produce a more attractive ornament in the large-seed patch B (labeled "habitat B"). Hence, the ornament functions as an indicator of local adaptation.

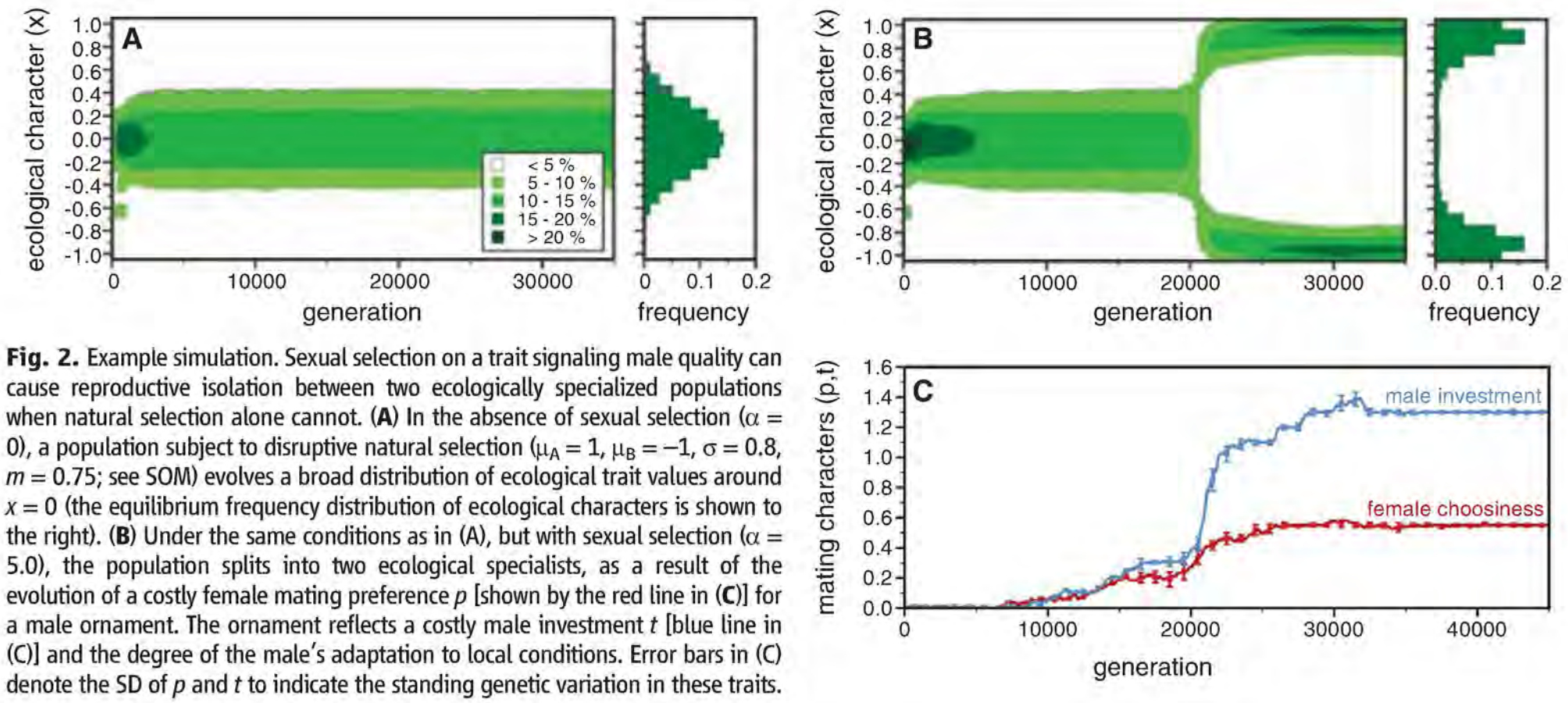

Fig. 2. Example simulation. Sexual selection on a trait signaling male quality can cause reproductive isolation between two ecologically specialized populations when natural selection alone cannot. (**A**) In the absence of sexual selection ($\alpha = 0$), a population subject to disruptive natural selection ($\mu_A = 1$, $\mu_B = -1$, $\sigma = 0.8$, $m = 0.75$; see SOM) evolves a broad distribution of ecological trait values around $x = 0$ (the equilibrium frequency distribution of ecological characters is shown to the right). (**B**) Under the same conditions as in (A), but with sexual selection ($\alpha = 5.0$), the population splits into two ecological specialists, as a result of the evolution of a costly female mating preference p [shown by the red line in (**C**)] for a male ornament. The ornament reflects a costly male investment t [blue line in (C)] and the degree of the male's adaptation to local conditions. Error bars in (C) denote the SD of p and t to indicate the standing genetic variation in these traits.

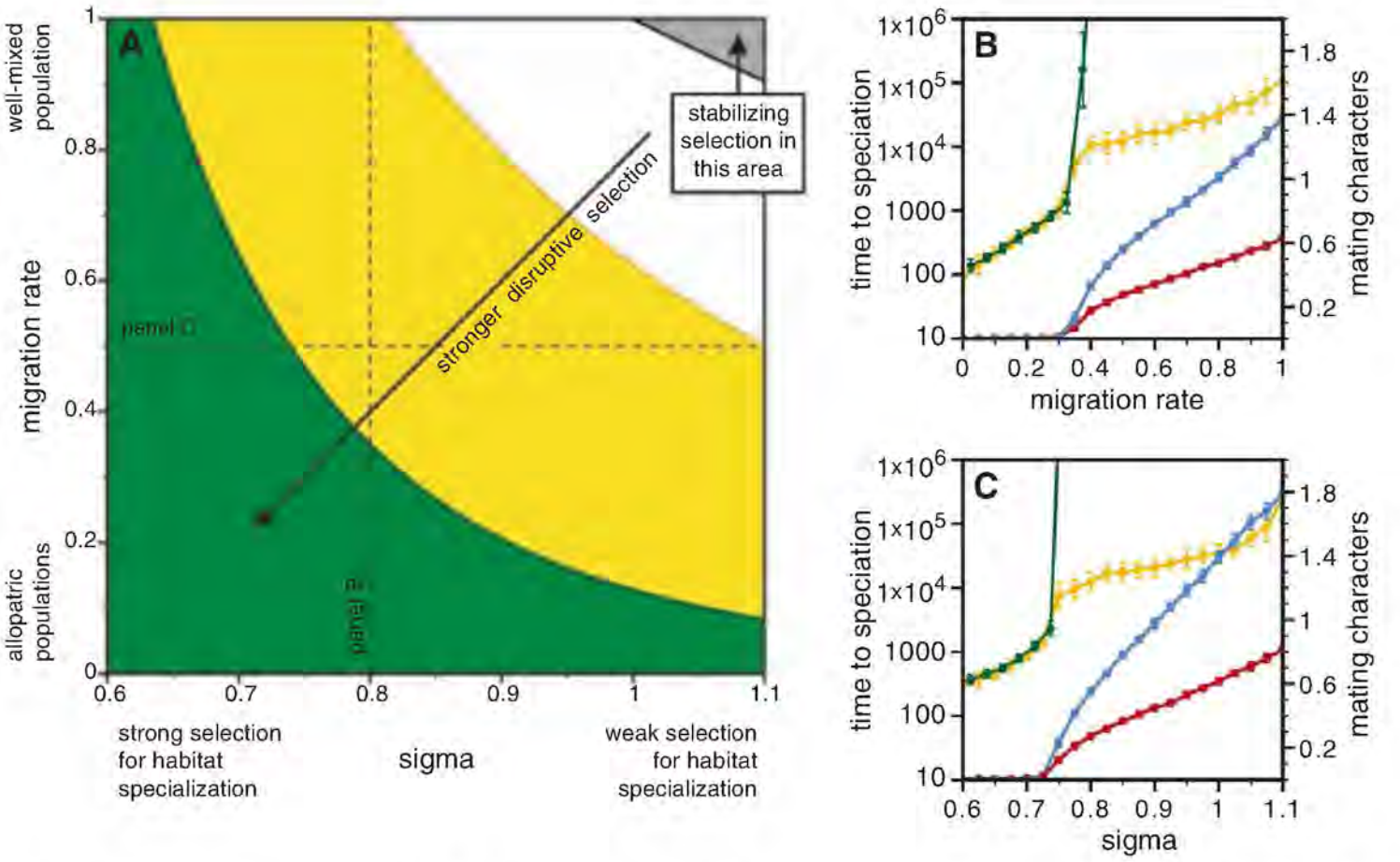

Fig. 3. Effect of ecological parameters on the rate of speciation. (**A**) Without sexual selection, ecological disruptive selection must be strong to induce speciation (green area). When mate choice reinforces ecological disruptive selection, speciation can occur under a broader range of parameters (yellow area). Below the yellow contour, speciation occurred within 10^5 generations in more than 50% of the simulations. (**B** and **C**) Orthogonal transects through parameter space illustrate a sharp increase of the time to speciation (green lines, in the absence of sexual selection) above a certain rate of migration [(B), $m > 0.3$] and below a critical strength of selection on the ecological character [(C), $\sigma > 0.75$]. With sexual selection, the time to speciation (yellow lines) increases gradually: As m and σ increase and ecological disruptive selection becomes weaker, higher values of the mating characters (red, female choosiness; blue, male investment into ornament expression) are required for the population to split. Points are mean ± SD (denoted by error bars) over 20 replicate simulations; other parameters are the same as those in Fig. 2.

intensity of stabilizing selection within habitats (σ). Reduced migration between habitats (lower m) and increased selection for ecological specialization (lower σ) both result in stronger disruptive ecological selection across habitats on the population as a whole (see SOM). Without the help of sexual selection, extreme combinations of parameters are required to induce speciation (Fig. 3, green area), but when mate choice based on local adaptation is added, the constraints on ecological parameters are considerably relaxed. Even relatively weak ecological disruptive selection can be intensified by sexual selection up to the level that is required for ecological speciation (Fig. 3, yellow area).

Natural and sexual selection are often depicted as opposing forces, but they can work in concert (*25*, *26*). Our model highlights how natural and sexual selection reinforce each other's actions in the context of adaptive speciation. Spatially heterogeneous selection pressures and migration between habitats can support the accumulation of genetic variation in ecological characters. Females enjoy durable benefits from choosing locally adapted males, unlike in populations that experience directional selection, where fitness variation is quickly depleted once sexual selection becomes stronger (*16*, *25*–*27*, *29*, *30*). Once a mating preference for locally adapted partners has evolved, sexual selection reinforces assortative mating and lowers the fitness of hybrids. This twofold effect of mate choice on pre- and post-zygotic reproductive isolation is likely to extend to cases where mate choice depends on direct benefits. Disruptive ecological selection could also be amplified by intrasexual selection, if local adaptation interferes with displays of condition that are used as signals in contests. Sexual selection would not be quite as effective in facilitating speciation in that case, however, because intrasexual selection does not necessarily strengthen assortative mating.

Our model differs from existing models of speciation by sexual selection in that it does not require the divergence of mating preferences between incipient species. Instead, gene flow between species is suppressed as a result of the genotype-by-environment interaction that determines mate attractiveness. Speciation on the basis of divergence of preferences and mating signals is fraught with complications due to the difficulty of supporting stable variation in mating preferences and maintaining linkage disequilibrium between mating traits and ecological characters (*3*–*6*, *9*, *10*, *13*, *14*); these issues are irrelevant to our model. In our model, incipient species only differ in ecological characters and not with respect to sexual preferences or ornamentation. Accordingly, speciation is more cryptic than in traditional models of speciation by sexual selection, at least during and shortly after the speciation process. In the long run, one would expect cryptic reproductively isolated habitat specialists to accumulate noticeable differences and species recognition traits.

Our results address a long-standing critique of models of sympatric speciation (*3*, *4*, *6*), which often rely on magic traits (*5*) to link ecological performance and assortative mating. In the case of host race specialization and comparable ecological contexts, it is widely recognized that ecology and mate choice are intimately intertwined. However, by lack of a general explanation for their presence, strong associations between ecological specializations and mating behavior are often dismissed as unlikely. Sexual selection acting on indicators of local adaptation could provide such a general explanation, as is increasingly being illustrated by empirical studies examining mate choice in its ecological context [(*10*) and references therein]. Local adaptation and the maintenance of ecologically relevant variation are ubiquitous in natural populations. Such variation can serve as raw material for adaptive mate choice whenever sexual ornaments reflect performance under the local ecological conditions. Sexual selection and disruptive ecological selection can then reinforce each other, eventually leading to ecologically specialized and reproductively isolated sister species. Therefore, the scope for ecological speciation may not be limited by the presence of fortuitous pleiotropy between ecological and mating traits, but rather by the evolution of reliable signals of local adaptation from which such pleiotropy inevitably emerges.

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Figs. S1 to S3
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Structure of the LKB1-STRAD-MO25 Complex Reveals an Allosteric Mechanism of Kinase Activation

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The LKB1 tumor suppressor is a protein kinase that controls the activity of adenosine monophosphate–activated protein kinase (AMPK). LKB1 activity is regulated by the pseudokinase STRADα and the scaffolding protein MO25α through an unknown, phosphorylation-independent, mechanism. We describe the structure of the core heterotrimeric LKB1-STRADα-MO25α complex, revealing an unusual allosteric mechanism of LKB1 activation. STRADα adopts a closed conformation typical of active protein kinases and binds LKB1 as a pseudosubstrate. STRADα and MO25α promote the active conformation of LKB1, which is stabilized by MO25α interacting with the LKB1 activation loop. This previously undescribed mechanism of kinase activation may be relevant to understanding the evolution of other pseudokinases. The structure also reveals how mutations found in Peutz-Jeghers syndrome and in various sporadic cancers impair LKB1 function.

Loss-of-function mutations in the tumor suppressor LKB1 cause the rare inherited disease Peutz-Jeghers syndrome (PJS) in humans (*1*) and are associated with various sporadic cancers, in particular non–small cell lung cancer (*2*). One prominent function of LKB1 is to ensure that growth and division are coupled to the availability of cellular energy. LKB1 phosphorylates and activates the adenosine monophosphate–activated protein kinase (AMPK) when energy levels are low, thereby leading to inhibition of signaling pathways that promote proliferation (*3*). The therapeutic effects of AMPK-activating drugs (e.g., metformin) on tumor growth (*4*) or blood glucose levels (*5*) are dependent on activation of AMPK by LKB1. Another key role of LKB1 is to control cell polarity, which may be mediated by AMPK (*6*) or by a group of AMPK-related protein kinases, including microtubule affinity-regulating kinases (MARKs, homologous to the *Caenorhabditis elegans* kinase Par-1) (*7*) that are also phosphorylated and activated by LKB1 (*8*).

In cells, LKB1 is found in a 1:1:1 heterotrimeric complex with the pseudokinase STRAD (Ste20-related adaptor) (*9*) and the scaffolding MO25 (mouse protein 25) (*10*). There are two closely related human isoforms of both STRAD (STRADα and STRADβ) and MO25 (MO25α and MO25β) that similarly interact with LKB1 (*11*). Unlike the majority of protein kinases, which are regulated by phosphorylation, LKB1 is activated by binding to STRAD and MO25 (*11*, *12*) through an unknown, phosphorylation-independent, molecular mechanism. Structural analysis of MO25α reveals a helical-repeat, horseshoe-shaped protein that interacts with the C-terminal WEF (Trp-Glu-Phe) motif of STRADα through a hydrophobic pocket located on its convex C-terminal surface (*13*). The structure of STRADα complexed with MO25α reveals additional interactions between the concave surface of MO25α and the regulatory αC helix of STRADα (*14*). STRADα, despite being a catalytically inactive pseudokinase, adopts a closed conformation typical of fully active protein kinases. The closed conformation of STRADα is maintained through its cooperative binding to adenosine triphosphate (ATP) and MO25α. Mutations that inhibit binding to ATP and MO25α prevent LKB1 activation, which suggests that the active conformational state of STRADα may be required for activation of LKB1 (*14*).

We report the crystal structure of the LKB1-STRADα-MO25α heterotrimeric complex. We used an insect cell expression system to produce an active core LKB1-STRADα-MO25α heterotrimeric complex, comprising the kinase domain of LKB1 (residues 43 to 347), complexed with the pseudokinase domain of STRADα (residues 59 to 431) and full-length MO25α (figs. S1 and S2). The crystal structure of the heterotrimeric complex with a catalytically inactive mutant of LKB1 ($Asp^{194} \rightarrow Ala$, preventing Mg^{2+} ion binding but not assembly of the complex; fig. S2B) in complex with the ATP analog adenyl-5′-yl imidodiphosphate (AMP-PNP) was solved and refined to 2.65 Å (table S1). There are two heterotrimeric complexes in the asymmetric unit displaying similar conformations (RMSD = 0.5 Å on 791 Cα atoms). Both STRADα and LKB1 are in complex with AMP-PNP, displaying binding modes typical of other protein kinases (fig. S3) (*15*).

The LKB1 heterotrimer has an overall compact globular shape with considerable interactions among all of the three subunits (Fig. 1A and fig. S4). The pseudokinase domain of STRADα binds to the kinase domain of LKB1. The horseshoe-shaped MO25α acts as a scaffold for assembly of the heterotrimer by binding both LKB1 and STRADα through highly conserved residues on the concave face of its helical repeats (Fig. 1A and fig. S4B). MO25α binds to STRADα through a large (2930 $Å^2$) interface centered on the regulatory helix αC of STRADα (Fig. 1A). The structure of the STRADα-MO25α complex within the heterotrimer is similar to the binary STRADα-MO25α complex structure (*14*) (RMSD = 0.5 Å on 529 Cα atoms; fig. S5), including ordered electron density for the STRADα C-terminal WEF motif interacting with a pocket on MO25α (*13*, *14*). The remaining MO25α concave surface is engaged in contacts (1580 $Å^2$) with the LKB1 activation loop, helix αI, and the C terminus of helix αC (Fig. 1A and fig. S4). The interface between LKB1 and STRADα mainly involves the C lobe of STRADα and both N and C lobes of LKB1 (1840 $Å^2$; Fig. 1C and fig. S4) and is comparable in size to the interaction between LKB1 and MO25α.

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Activation of LKB1 is thought to be mediated through a conformational change triggered by binding to STRAD and MO25 (*11*, *12*). The structure of the core LKB1 heterotrimer is consistent with this, as LKB1 lacks phosphorylation of the activation loop yet adopts an active conformation (fig. S6). The LKB1 αC helix is rotated into the canonical closed conformation, forming the conserved salt bridge between Lys^{78} (the so-called VAIK motif in subdomain II) and Glu^{98} (αC helix in subdomain III; fig. S6). This active conformation of LKB1 appears to be achieved through contributions of both STRADα and MO25α.

Structural elements on the STRADα C lobe that normally make up the substrate binding site in active protein kinases [i.e., the αG helix (*16*) and the p+1 loop (*15*)] interact with LKB1 (Fig. 1B and fig. S7). Furthermore, the activation loop of STRADα interacts with both N and C lobes of the LKB1 kinase domain (Fig. 1B). Mutation of residues in the substrate-binding region of STRADα (Leu^{241} in the p+1 loop and Gln^{251} in the αEF-αF loop) inhibit interaction with LKB1, whereas mutation of Gln^{286} (αG helix) has a moderate effect (Fig. 2A). Mutation of Gln^{251} (αEF-αF loop), alone or in combination with a mutation on STRADα that disrupts the MO25α-STRADα interaction (Tyr^{185} → Phe) (*14*), suppresses LKB1 activation without affecting complex assembly (Fig. 2B). The reciprocal mutation of Arg^{74} on LKB1 that forms a hydrogen bond to Gln^{251} (Fig. 1B) also impairs the ability of STRADα to activate LKB1 without affecting complex assembly (Fig. 2D). These experiments suggest that binding of STRADα to the β2-β3 loop of LKB1 exerts a conformational effect that promotes LKB1 activation.

Comparison of the active and inactive structures of cyclin-dependent kinase 2 and epidermal growth factor receptor reveals that the β2-β3 loop undergoes large positional shift upon activation (fig. S8). Furthermore, β2-β3 loop interactions of RAF are important for its dimerization-dependent activation (*17*) (fig. S8C). Interestingly, residues on the STRADα activation loop (His^{231} and Phe^{233}) bind to β7-β8 (C lobe) and β2-β3 (N lobe) of LKB1, respectively (Fig. 1B), perhaps aiding in the positioning of the N and C lobes relative to each other. In the absence of MO25α, mutation of His^{231}, Phe^{233}, or both prevented STRADα from binding to LKB1 (Fig. 2A). However, in the presence of MO25α, only the His^{231}-Phe^{233} double mutant reduced LKB1 activation and complex

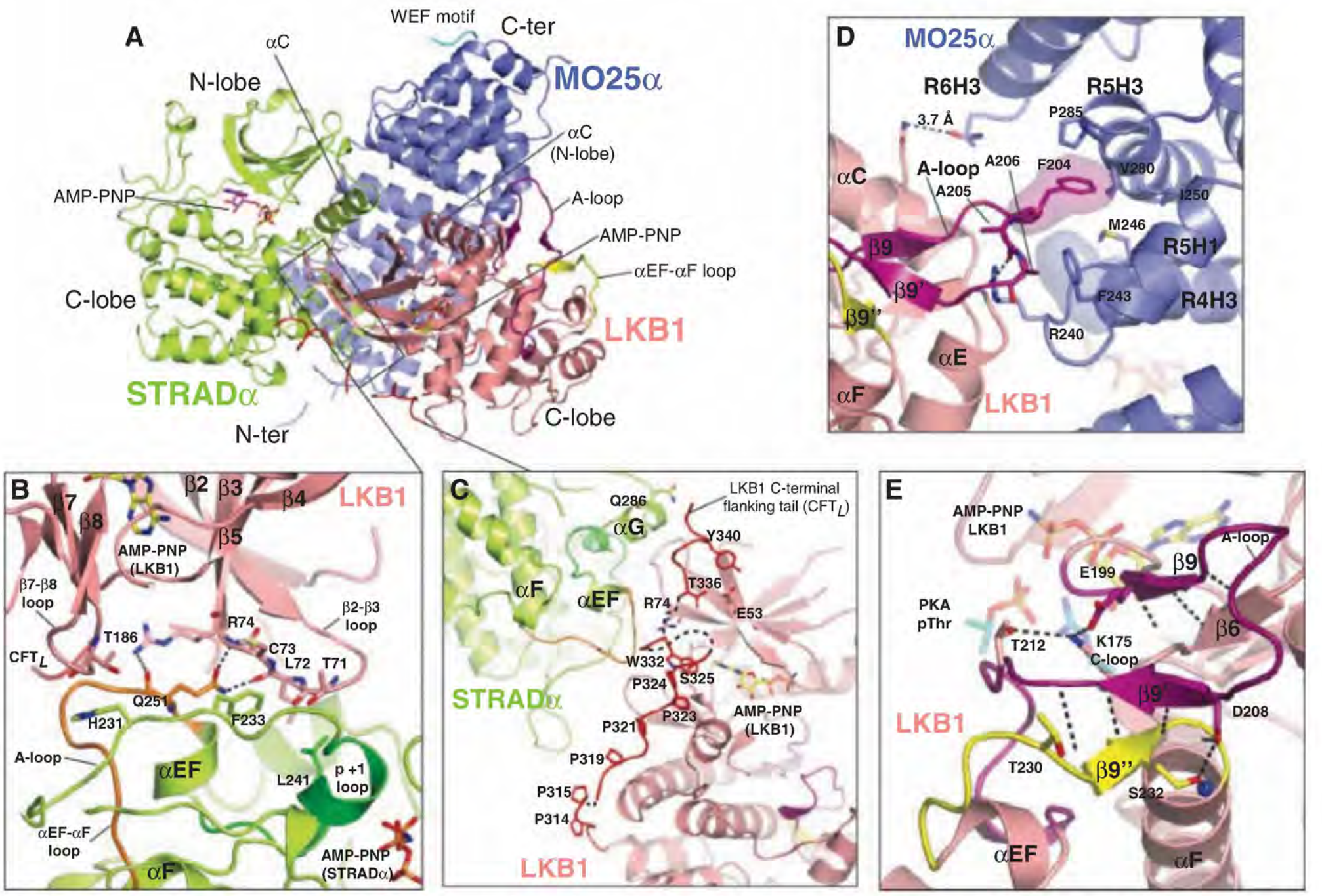

Fig. 1. Overall structure and LKB1-STRADα-MO25α complex interactions. (**A**) Cartoon representation of the heterotrimeric complex and two bound AMP-PNP molecules are shown in stick representations (LKB1, yellow carbons; STRADα, magenta carbons). The γ-P for AMP-PNP bound to LKB1 was not visible because of disorder. The WEF motif at the C terminus of STRADα, for which connectivity could not be unambiguously identified because of disorder of the linkers, is shown in cyan. (**B**) Detailed view of LKB1-STRADα interaction. STRADα p+1 and αEF-αF loops are colored green and orange, respectively. (**C**) Interaction of the LKB1 CFT_L with STRADα and LKB1 N and C lobes. The proline-rich CFT_L is colored red. (**D**) Detailed view of LKB1-MO25α interaction. The LKB1 activation loop is colored magenta. (**E**) Detailed view of LKB1 A-loop interactions. Backbone interactions are shown as dashed lines. Residues Asp^{208}, Thr^{230}, and Ser^{232} mutated in PJS are labeled and their side chains displayed. A salt bridge between Glu^{199} and Lys^{175} (dashed line) represents the interaction of the LKB1 activation segment with its catalytic loop (C-loop). The corresponding interaction found in PKA (PDB ID 1ATP) between the phosphorylated Thr^{197} (pThr) and Arg^{165} is also shown, with PKA residues represented as transparent sticks (carbon atoms colored cyan). The typical "activatory" threonine (Thr^{202}) present in the LKB1 A-loop is labeled. Secondary structure elements are labeled according to the structure of PKA (*15*).

assembly (Fig. 2B). Combining the His^{231}-Phe^{233} double mutant with the Tyr^{185} mutation that disrupts interaction with MO25α (*14*) resulted in a mutant STRADα that did not form a complex with LKB1 and MO25α (Fig. 2B). These experiments define the regions on STRADα that interact with LKB1 and MO25α and contribute to the assembly of an active LKB1 complex.

A common feature of many protein kinase folds is a C-terminal flanking tail (CFT) that interacts with the N-terminal lobe of the kinase (*18*). This tail either serves directly as an autoactivatory mechanism or provides a docking site for regulatory interacting partners (*18*). LKB1 has a proline-rich CFT_L (residues 311 to 347) that runs along the STRADα-LKB1 interface and interacts with the STRADα helix αG as well as the LKB1 N-terminal lobe (Fig. 1, A and C). An LKB1 mutant lacking part of the CFT_L motif (ΔCFT_L, residues 1 to 318) failed to interact with STRADα in the absence of MO25α (Fig. 2C). Mutation of individual residues in or interacting with the CFT_L (Trp^{332}, Tyr^{340}, and Arg^{74}) did not affect assembly of the LKB1 complex; however, LKB1(ΔCFT_L) formed a complex with reduced catalytic activity when coexpressed with STRADα and MO25α (Fig. 2D). As mentioned above, mutation of Arg^{74} (which interacts with the CFT_L but also with STRADα; Fig. 1, B and C) on LKB1 abolished interaction with STRADα in the absence of MO25α (Fig. 2C) and reduced the catalytic activity of the complex (Fig. 2D). The CFT_L also contains two phosphorylation sites: Ser^{325} (*19*), which may be phosphorylated by ERK (*20*), and Thr^{336}, an autophosphorylation site (*19*). These sites appear not to directly influence LKB1 catalytic activity (*19*) or complex assembly (*11*) but could affect association of LKB1 with substrates or regulators. These results reveal an important role for the CFT_L in LKB1-STRADα interactions and LKB1 activity and are suggestive of a potential role for other, as yet unidentified, LKB1 regulators that may make use of this region.

Most protein kinases are activated by phosphorylation of their activation loop, producing a conformation competent for substrate binding (*21*). Despite the lack of activating phosphorylation, the LKB1 activation loop is well ordered (fully defined by electron density) and adopts a conformation typical of loops from active protein kinases (Fig. 1A and fig. S6). Key to this is the interaction of Phe^{204} from the LKB1 activation loop with a hydrophobic pocket on the concave surface of MO25α (Fig. 1D). Individual mutation of Phe^{204} did not affect LKB1 complex formation or activity (Fig. 2D). However, mutation of Phe^{204} together with Arg^{74}, a residue required for LKB1-STRADα interaction (Figs. 1B and 2C), resulted in LKB1 species that were incapable of forming a heterotrimeric complex (Fig. 2D). Additional interactions occur between Arg^{240} and Phe^{243} on MO25α with the backbone of Ala^{205}

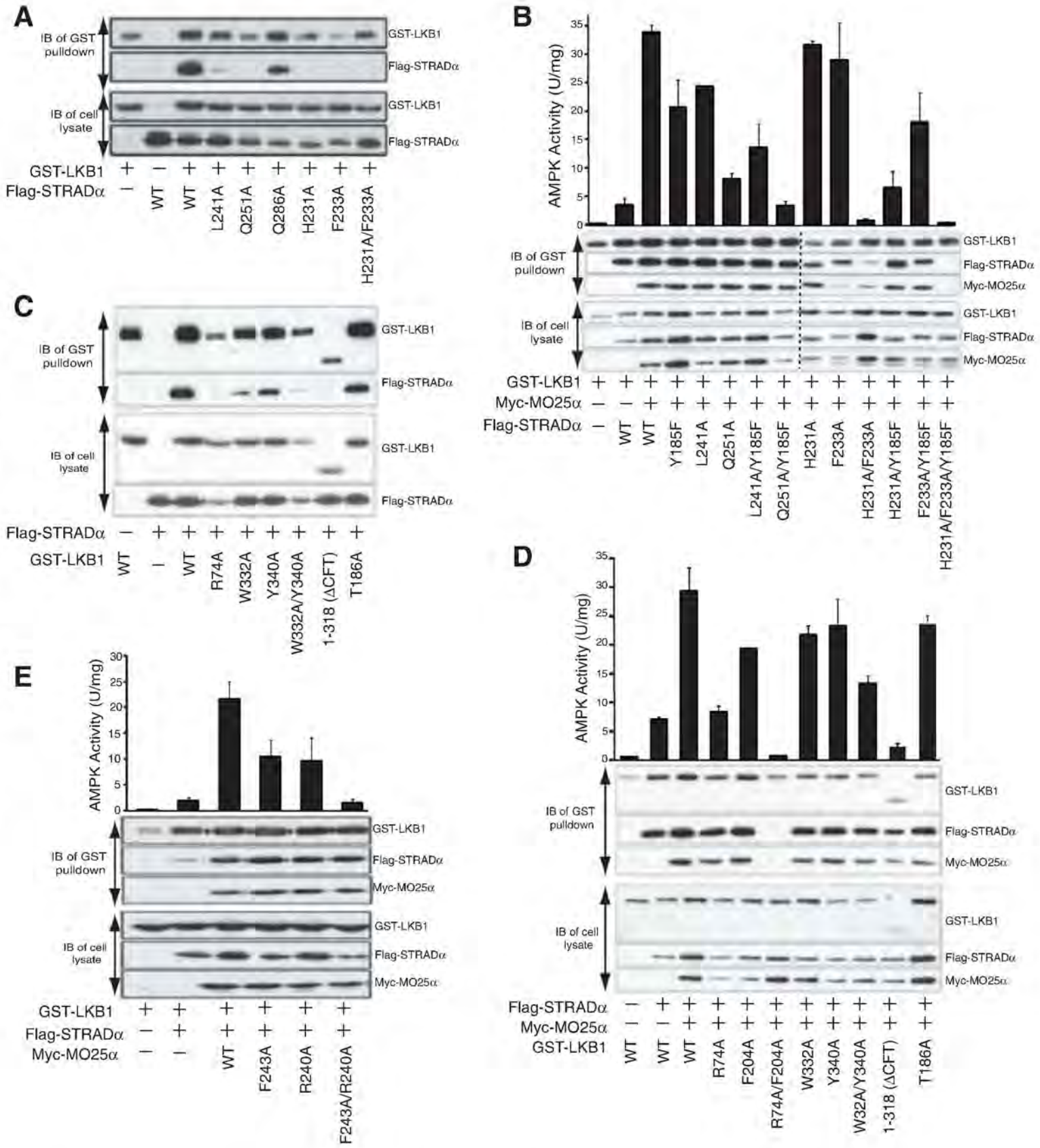

Fig. 2. Characterization of the LKB1-STRADα-MO25α interactions and LKB1 activation. (**A** and **C**) The indicated constructs of GST-LKB1 and Flag-STRADα were expressed in 293 cells in the absence of MO25α. Cells at 36 hours after transfection were lysed and GST-LKB1 was affinity-purified on glutathione-Sepharose. The purified GST-LKB1 preparation (upper panels) as well as the cell extracts (lower panels) were immunoblotted with the indicated antibodies. Similar results were obtained in three separate experiments. (**B**, **D**, and **E**) 293 cells were cotransfected with the indicated constructs of GST-LKB1, Flag-STRADα, and Myc-MO25α. Cells at 36 hours after transfection were lysed and GST-LKB1 was affinity-purified and assayed for the ability to activate heterotrimeric AMPK complex expressed in *Escherichia coli* (see supporting online material). Kinase activities are representative of three independent assays carried out in triplicate (error bars represent SD for a single triplicate experiment). Affinity-purified GST-LKB1 preparation (upper panels) as well as cell extracts (lower panels) were immunoblotted with the indicated antibodies.

and Ala^{206} of LKB1; Arg^{240} and Phe^{243} act as a molecular "peg" to orient the activation loop of LKB1 and stabilize its active conformation (Fig. 1D). Although mutation of both Arg^{240} and Phe^{243} did not affect the ability of MO25α to interact with STRADα and LKB1, the resulting complex is inactive, establishing the importance of this interaction in stimulating LKB1 (Fig. 2E). Although MO25α alone is known not to form a stable complex with LKB1 (*10*, *11*), in the presence of STRADα, MO25α stabilizes the activation loop of LKB1 in an optimal conformation required for phosphorylation of substrates. The position of Thr^{212} in the LKB1 activation loop is equivalent to that of the activation loop phosphothreonine of protein kinases that require activatory phosphorylation (Fig. 1E). However, Glu^{199} (β9) replaces the negative charge that would otherwise be provided by the phosphate group and is within hydrogen-bonding distance of Lys^{175} (Fig. 1E). A PJS mutation, Glu^{199} → Lys, impaired LKB1 catalytic activity, although a less severe PJS mutation (Glu^{199} → Gln) did not impair LKB1 activity (fig. S9).

Dozens of human genes code for protein kinases that lack essential residues in their catalytic machinery and have been termed pseudokinases (*22*, *23*). Some are in fact catalytically competent (*24*), but others are either incapable of binding ATP (*25*) or incapable of catalyzing phosphoryl transfer (*14*). It is possible that STRADα evolved from a catalytically competent protein kinase that phosphorylated LKB1. This notion is supported by the observation that STRADα interacts with LKB1 through structural elements in its C lobe that are normally used by active protein kinases to bind their substrates (e.g., the p+1 loop/αG helix). More important, protein kinases generally need to be in their active conformation to bind their substrates, and STRADα appears to adopt an "active" conformation stabilized through ATP and MO25 to activate LKB1 (*14*).

In order for LKB1 to phosphorylate AMPK, the active-site cleft of LKB1 must be accessible. Indeed, the structure of the heterotrimer shows that the C-terminal lobe of LKB1 is not engaged in interactions with STRADα or MO25α. Moreover, the region around the γ-phosphate (disordered in our structure) of ATP is solvent-exposed in LKB1 (fig. S7C).

Mutations in the gene encoding LKB1 are the main cause of PJS (*1*), and at least 51 missense mutations have been mapped to the LKB1 kinase domain and the CFT_L loop (Fig. 3, table S2, and fig. S10). We have characterized the effects that these mutations have on the ability of LKB1 to form active heterotrimeric complexes with STRADα and MO25α (*11*) (fig. S9). The majority of mutations are residues important for the structural integrity of LKB1 (Fig. 3A). There are two hydrophobic clusters, named hydrophobic cluster 1 (Phe^{157}, Leu^{242}, Leu^{285}, Trp^{308}) and hydrophobic cluster 2 (Leu^{164}, Ile^{177}, and Leu^{182}) (Fig. 3A). Many of these mutations resulted in low LKB1 expression levels, and all of these LKB1 mutants were incapable of forming active complexes with

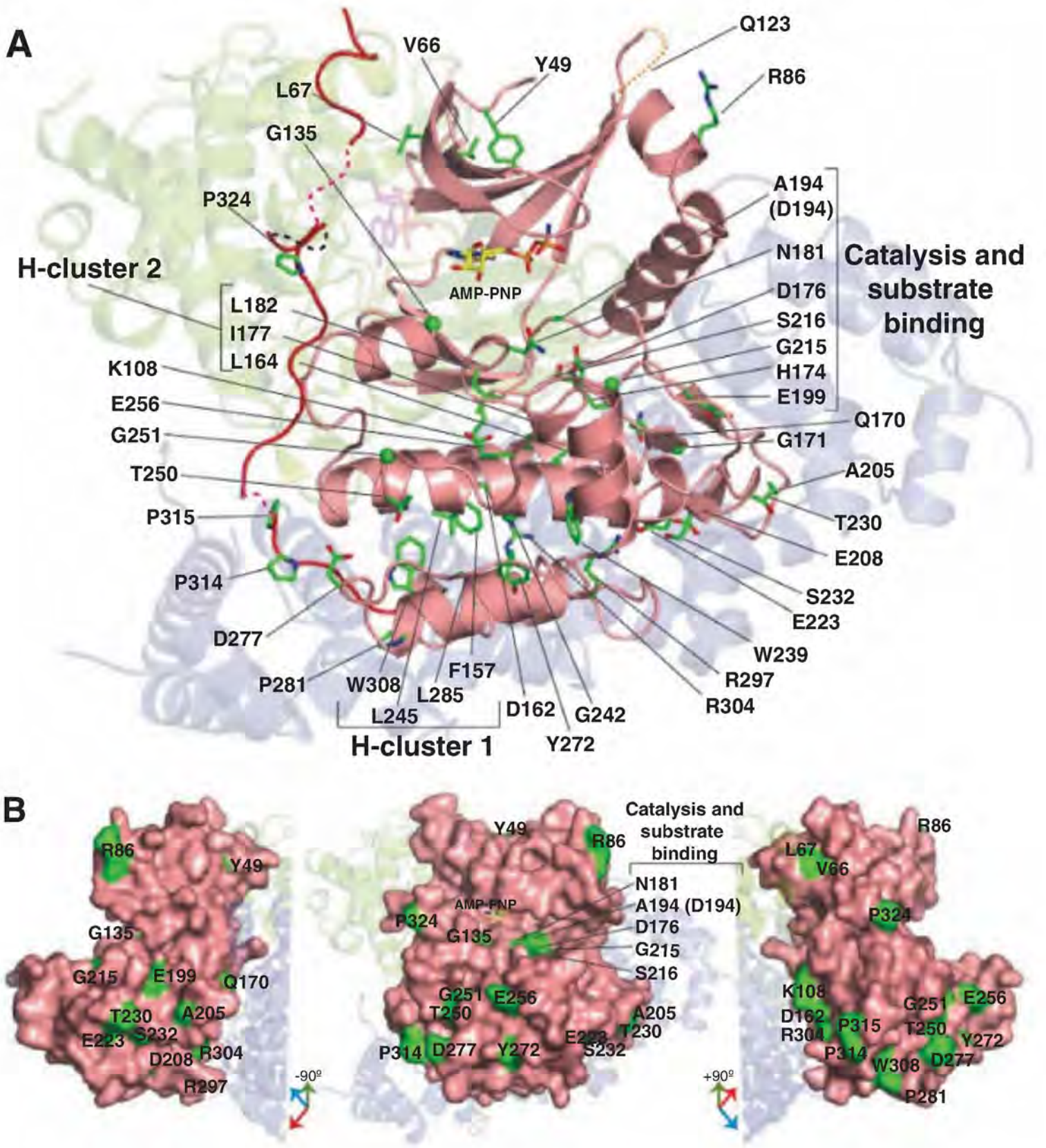

Fig. 3. Map of oncogenic mutations on the LKB1 kinase domain and the CFT_L. (**A**) Location of LKB1 residues that are mutated in PJS and other types of cancer. The CFT_L region is colored red. Dashed lines represent areas that were not well defined by electron density. (**B**) Surface-exposed residues that are mutated in PJS and other types of cancer.

STRADα and MO25α (Fig. 3 and table S2). In addition, at least 10 mutations involve residues required for catalysis or substrate binding (Fig. 3). Although these mutants properly assembled into complexes with STRADα and MO25α, these were devoid of catalytic activity (fig. S9 and table S2). Other mutations present in the activation loop ($Ala^{205} \rightarrow Thr$, $Asp^{208} \rightarrow Asn$), the αEF-αF loop ($Thr^{230} \rightarrow Pro$, $Ser^{232} \rightarrow Pro$), and the CFT_L region ($Pro^{314} \rightarrow His$, $Pro^{315} \rightarrow Ser$, $Pro^{324} \rightarrow Leu$) did not affect the ability of LKB1 to assemble into active complexes. There are also a number of oncogenic mutations in solvent-exposed residues ($Arg^{86} \rightarrow Gly$, $Gln^{123} \rightarrow Arg$, $Tyr^{272} \rightarrow His$, $Asp^{277} \rightarrow Tyr$) that do not affect complex assembly or activity (fig. S9 and table S2). Thus, out of 51 mutations analyzed, 18 formed complexes with STRADα and MO25α that showed LKB1 activity (table S2). Assuming these are cancer-driving rather than passenger mutations, some of these mutations may be involved in interacting with other regulators or substrates of the LKB1 pathway.

Our study reveals how LKB1 is activated. In addition to STRADα binding, MO25α plays a crucial role in stabilizing the LKB1 activation loop in a conformation required for phosphorylation of substrates. Thus, a previously unrecognized role of STRADα is to promote interaction between MO25α and LKB1. This represents a mechanism by which kinases may be regulated allosterically, independent of activation loop phosphorylation. The LKB1 complex structure also shows how cancer mutations affect LKB1 function by impairing complex assembly, catalytic activity, and potential interactions with substrates or regulators. Finally, our findings provide insights into how certain pseudokinases may have evolved, by retaining active conformations that allow interactions similar to those by which active kinases bind their substrates.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/1178377/DC1
Materials and Methods
Figs. S1 to S12
Tables S1 and S2
References

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The Subtle Transmission of Race Bias via Televised Nonverbal Behavior

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Compared with more explicit racial slurs and statements, biased facial expressions and body language may resist conscious identification and thus produce a hidden social influence. In four studies, we show that race biases can be subtly transmitted via televised nonverbal behavior. Characters on 11 popular television shows exhibited more negative nonverbal behavior toward black than toward status-matched white characters. Critically, exposure to prowhite (versus problack) nonverbal bias increased viewers' bias even though patterns of nonverbal behavior could not be consciously reported. These findings suggest that hidden patterns of televised nonverbal behavior influence bias among viewers.

In contemporary Western culture, most people claim that they do not behave in a racially biased fashion, and America recently elected its first black president. Yet recent claims of a race-blind society are contradicted by studies of race biases, in which people exhibit more positive responses to one race than another (*1*–*6*). To the extent that race biases are communicated explicitly, egalitarian norms encourage observers to discount them as a valid source of knowledge (*7*, *8*). For example, observers can consciously debate and publicly denounce race-biased aggressive acts, verbal statements, and hiring procedures, thus resisting conformity to these explicit race biases. However, race biases are often communicated subtly via facial expressions and body language (*2*–*6*). Indeed, mounting evidence suggests that Americans' nonverbal behavior favors white over black persons (*2*, *4*, *9*–*12*). Because nonverbal behavior is "off the record" and can be difficult to identify unambiguously, exposure to nonverbal race bias may undermine norm-driven correction processes and hence may exert a social influence (*13*, *14*). Specifically, exposure to nonverbal race bias, via evaluative conditioning, may cause perceivers to associate race with affect and thus exhibit race bias themselves (*15*–*18*). We examined the prevalence, subtlety, and impact of nonverbal race bias in four studies. We observed that nonverbal race bias occurs on television and that exposure to this televised bias accounts in part for white viewers' own race bias, as assessed with reaction-time and self-report measures. Moreover, patterns of nonverbal bias were influential even when they could not be consciously reported.

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Table 1. Study 1: Featured (but unseen) character ratings by race. Means ± SD; *t*(28).

Character rating	White character mean	Black character mean	*t* value	*P* value	*rpb*
Favorable nonverbal response	0.16 ± 0.24	−0.04 ± 0.28	2.08	0.047*	0.37
Favorable verbal response	0.17 ± 0.20	0.04 ± 0.34	1.35	0.19	0.25
Perceived attractiveness	4.88 ± 1.16	4.74 ± 1.04	0.35	0.73	0.07
Perceived sociability	4.79 ± 0.66	5.14 ± 0.88	−1.22	0.23	0.22
Perceived kindness	4.54 ± 0.77	4.75 ± 0.48	−0.90	0.38	0.17
Perceived intelligence	4.92 ± 1.05	5.12 ± 0.93	−0.56	0.58	0.10

The first study examined whether nonverbal race bias existed across 11 television shows that reach millions of Americans on a weekly basis (*19*). To isolate race-based bias, we only examined popular television shows that included recurring white and black characters whose status could be roughly equated. We sampled at least three episodes from each of 11 shows that met our criteria (*19*). For each of 30 characters, we selected three 10-s clips from each episode according to a priori criteria. We selected the first clip from the first 5 min of each episode in which the character appeared in an interpersonal interaction (with a white person) lasting at least 10 s. These same criteria were applied to a clip from the "middle" 5 min and the last 5 min of each episode (nine clips in total).

We edited these clips to remove the audio track and the featured character. For example, the character Alexx of *CSI: Miami* was cropped out of her clips so that only the other characters could be seen—this procedure prevented any race-related demand characteristics (*20*). These cropped and silent video clips were shown to 23 white undergraduate judges who had not seen any of the 11 shows, as determined by responses to an e-mailed survey (*21*). For each cropped and silent clip, judges rated (with –3 to +3 scales) the extent to which the unseen character was treated positively and liked by the other characters (*19*). These ratings were averaged across judges to index the degree to which each featured character elicited favorable nonverbal responses from other characters (table S1).

Compared with black characters, white characters elicited significantly more favorable nonverbal responses (Table 1). On only 2 of 11 shows did black characters elicit (slightly) more favorable nonverbal responses than white characters. To examine whether white and black characters in these shows differed on variables other than race, 17 white student judges (who reported watching most of the 11 shows) rated each featured character for attractiveness, sociability, kindness, and intelligence. For each judgment, agreement among the judges was high (all interrater α values > 0.85), so scores for each character were averaged across judges (table S1). White and black characters did not significantly differ on any of these variables (Table 1). To examine whether white and black characters elicited different verbal responses, 13 white undergraduate judges rated (on a –3 to +3 scale) the transcribed verbal content of each clip for the extent to which the speaking characters treated featured characters favorably (table S1). White and black characters did not differ in the elicitation of favorable verbal responses (Table 1). Finally, even after controlling for all character traits and favorable verbal responses in an analysis of covariance, white characters elicited more favorable nonverbal responses than did black characters, $F_{1,23} = 4.30$, $P = 0.05$, $rpb = 0.40$ (for correlations among character ratings, see table S2).

Nonverbal race bias was thus observed across 11 shows, each with an average weekly audience of 9 million, suggesting that many Americans are exposed to nonverbal race bias. These biases may occur for a variety of reasons: because actors spontaneously exhibit nonverbal bias, because biased nonverbal behavior is written into scripts, and/or because directors persuade actors to change their nonverbal behavior. Regardless, the bias appears on a number of popular television shows and thus may influence viewers. In study 2, we examined whether natural exposure to nonverbal race bias via television was related to viewers' own race associations. Exposure to subtle covariation between race and affect on television should produce associations in viewers [perhaps via evaluative conditioning (*15–18*)]. The implicit association test (IAT) (*3*) was used to assess viewers' race associations. Although there is debate about the extent to which IAT scores index implicit racial prejudice versus cultural knowledge (*22–25*), the IAT does measure psychological associations that predict race-related thought and behavior (*26*, *27*). (See study 4 for a replication with a different measure.)

For study 2, we computed nonverbal bias scores for each of the 11 shows by subtracting the favorable nonverbal response score for the black character(s) from that of the white character(s). Hence, higher numbers indicated more prowhite bias for a show ($M_{Show} = 0.10$, $range_{Show} = -0.08$ to 0.43). Exposure to nonverbal race bias scores were calculated for each of 53 white undergraduate participants by first determining which of the 11 shows they watched (via survey) and then averaging the nonverbal race bias scores for these shows [for this calculation, see (*19*)]. In an ostensibly separate study, participants completed a race IAT in which they identified faces as white or black and words as positive or negative—on trial block "w-p," participants used the same key to respond {"white" or "positive"} and another key to respond {"black" or "negative"}, whereas on trial block "b-p," the pairings were {"black" or "positive"} and {"white" or "negative"}. IAT scores were computed as the standardized difference in reaction times between block w-p ($M = 746.15$) and block b-p ($M = 993.81$) such that higher scores indicate faster responses to white-positive and black-negative than to white-negative and black-positive (*28*) (table S3).

As expected, more exposure to nonverbal bias was associated with greater IAT scores [$r(51) = 0.28$, $P = 0.047$]. To examine the possibility that the explicit verbal content on these shows was confounded with and accounted for effects of nonverbal content, we calculated verbal race bias scores for each show. We subtracted favorable verbal response scores (study 1) for black characters from those for white characters. These verbal race bias scores were averaged across each participant's regularly watched shows to form an "exposure to verbal bias" score. Exposure to verbal race bias was not significantly related to IAT scores [$r(51) = 0.15$, $P = 0.27$].

Alternatively, exposure to any nonverbal bias (e.g., toward attractive characters) might account for the study 2 findings. With the character ratings from study 1, we computed indices of exposure to nonverbal biases unrelated to race. For example, each character's favorable nonverbal response score (study 1) was multiplied by his or her perceived attractiveness score, and these scores were averaged within each show. Thus, shows with higher scores depicted especially positive nonverbal behavior directed toward attractive (versus unattractive) characters. We averaged these scores across the shows watched by each study 2 participant; the same procedure was followed for perceived sociability, kindness, and intelligence. Exposure to these alternative nonverbal biases was unrelated to viewers' race associations—this was true for attractiveness [$r(51) = 0.05$, $P = 0.73$], sociability [$r(51) = 0.16$, $P = 0.25$], kindness [$r(51) = 0.06$, $P = 0.70$], and intelligence [$r(51) = -0.11$, $P = 0.45$]. Finally, a partial correlation (pr) with nonracial biases and verbal race bias as covariates revealed a still-significant relation between exposure to nonverbal race bias and IAT scores [$pr(46) = 0.29$, $P = 0.048$].

The correlational design of study 2 leaves open several possibilities for causality, including that exposure to nonverbal bias influenced viewers' own bias or that viewers' own bias caused them to watch nonverbally biased programs. The

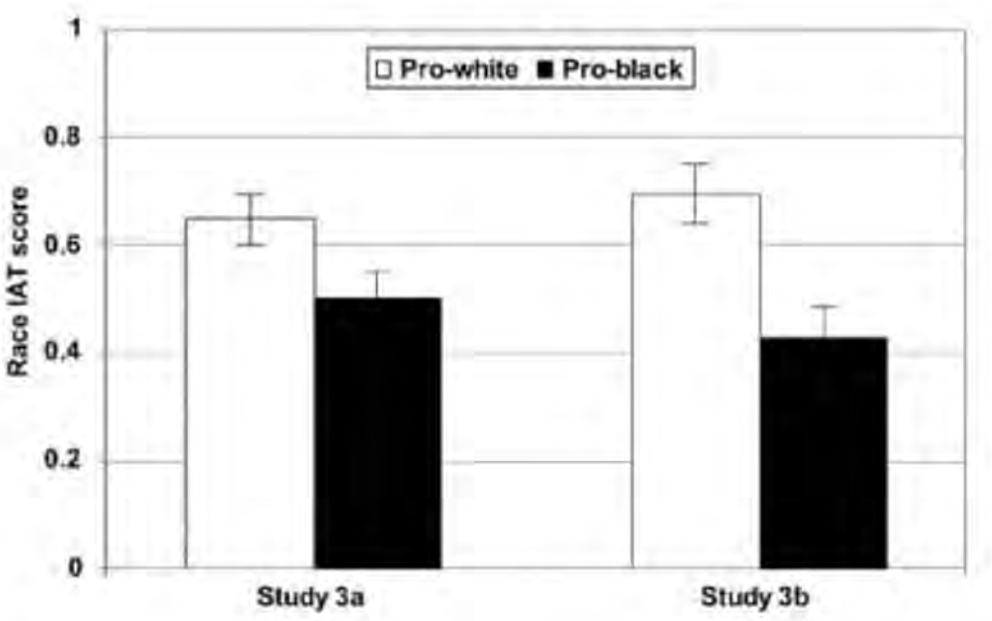

Fig. 1. Mean IAT scores in studies 3a and 3b as a function of exposure to nonverbal bias (prowhite or problack exposure). Error bars represent SEM.

focus here was on social influence, so we conducted several experiments to assess the causal influence of exposure to nonverbal race bias. In studies 3a (n = 62) and 3b (n = 35), white participants were exposed to one of two sets of silent video clips. In both experiments, the "prowhite" set depicted white characters eliciting favorable nonverbal behavior and black characters eliciting unfavorable nonverbal behavior (*6*). The "problack" set depicted the opposite pattern (these patterns were confirmed by independent judges) (*19*). To control for potential confounding variables in study 3a, the same characters appeared in the prowhite and problack sets. In study 3b, the prowhite and problack sets were matched for character attractiveness, sociability, kindness, and intelligence, as confirmed by independent student judges (table S4).

The procedure and measures were identical across studies 3a and 3b. In both studies, after exposure to one of the two sets of video clips (prowhite or problack), participants completed what they thought was a separate study but was actually the same IAT used in study 2 (for IAT calculations and component means, see table S3). As expected, participants exposed to the prowhite clips exhibited significantly higher (prowhite) IAT scores than participants exposed to the problack clips, and this was true for both study 3a ($F_{1,58}$ = 3.91, P = 0.05, rpb = 0.25) and study 3b ($F_{1,31}$ = 4.75, P = 0.04, rpb = 0.36) (Fig. 1). Thus, exposure to nonverbal race bias influenced perceivers' own race associations.

We have argued that nonverbal race bias exerts a particularly subtle influence because perceivers are unlikely to be aware of its presence. This does not mean that perceivers should have difficulty identifying nonverbal behavior per se but rather that they should have difficulty identifying a pattern of nonverbal race bias. Accordingly, we investigated whether people could consciously identify patterns of nonverbal race bias across each set of clips from study 3b. Twenty-two white participants were told that there was a hidden pattern across silent video clips which they then watched—half watched each set (prowhite or problack). After viewing these clips, participants were asked to indicate whether black characters had been treated better than white characters or the converse. Judgments were not different from chance (50%)—in each condition, 45% guessed that the clips were "problack." Hence, participants were unable to report the pattern of nonverbal behavior across clips, which suggested that nonverbal race bias exerts an unconscious influence.

In a fourth study, we further examined the causal influence of nonverbal race bias established in studies 3a and 3b. We added a control condition to assess the polarity of this influence; the control condition included clips from each of the other two sets and depicted equally positive nonverbal behavior directed toward white and black characters (*19*). Additionally, an affective priming measure (*4*, *29*) replaced the IAT. This measure assessed the degree to which subliminal images of black, white, or Asian faces sped responses to positive versus negative target images. For the 56 white participants in this study, differences in reaction time to positive versus negative objects were calculated for each prime (black, white, and Asian) to index affective associations (*29*) (for component means, see table S5).

A 3 (nonverbal bias) × 3 (prime race) analysis of variance (ANOVA) revealed only a significant interaction ($F_{4,106}$ = 3.13, P = 0.02) (Fig. 2). A priori contrasts revealed that white associations were more positive for participants exposed to prowhite nonverbal bias than to problack nonverbal bias ($F_{1,106}$ = 6.71, P = 0.01) or to the control condition ($F_{1,106}$ = 9.72, P = 0.002), whereas the last two conditions did not differ ($F_{1,106}$ = 0.09, P = 0.77). Black associations were more positive for participants exposed to problack nonverbal bias than to prowhite nonverbal bias ($F_{1,106}$ = 4.77, P = 0.03) or to the control condition ($F_{1,106}$ = 4.62, P = 0.03), whereas these last two conditions did not differ ($F_{1,106}$ = 0.001, P = 0.97). Asian associations did not differ by nonverbal bias condition (all F values < 1, P values > 0.36). Hence, the effects of nonverbal race bias seemed to be (i) specific to the races targeted in the nonverbal bias, (ii) of similar magnitude for prowhite and problack nonverbal bias, and (iii) largely due to the increased positivity of measured associations.

To examine whether nonverbal bias influenced feelings for particular characters, participants were asked (after the exposure phase) to rate how much they liked each character—the difference between liking for white (M = 4.21) and black characters (M = 4.54) indexed "relative liking" (*19*). An ANOVA revealed a main effect ($F_{2,53}$ = 13.65, P < 0.001). Participants in the control condition exhibited less relative liking (M = –0.33) for white characters than those in the prowhite condition (M = 0.46, P = 0.02), and less relative liking for black characters than those in the problack condition (M = –1.09; P = 0.03) (Bonferonni post hoc analyses). Hence, self-reported affect toward white and black characters was influenced by exposure to nonverbal bias. Moreover, greater relative liking for white over black characters was correlated with more positive white associations on the priming task (Table 2). Indeed, positive white associations accounted in part for the relation between exposure to prowhite nonverbal bias (versus the control) and relative liking (*19*).

Participants also completed a conventional measure of racial prejudice (the "attitudes toward blacks" self-report survey) (*30*). An ANOVA revealed that scores differed by exposure condition ($F_{2,53}$ = 3.21, P = 0.048). Those in the problack nonverbal bias condition exhibited significantly lower self-reported racial prejudice (M = 1.83) as compared with the prowhite condition [M = 2.22, t(33) = 2.08, P = 0.04], and the control condition [M = 2.26, t(33) = 2.66, P = 0.01]. Hence, exposure to problack nonverbal bias mitigated self-reported racial prejudice.

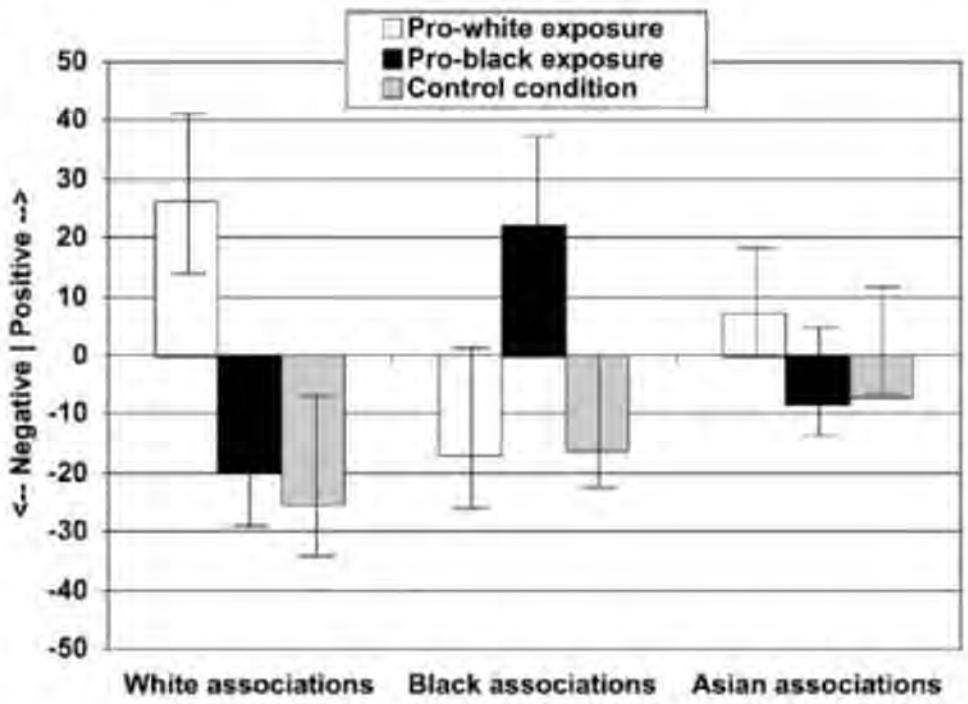

Fig. 2. Mean race-based associations as a function of exposure to nonverbal bias (prowhite exposure, problack exposure, or control condition). Higher numbers on the y axis indicate faster responses to positive (versus negative) targets. Error bars represent SEM.

Table 2. Study 4: Correlations among measures. P values in parentheses. More positive associations indicate faster responses to positive (versus negative) target images following a race prime. Character ratings index liking for white minus black characters. n = 53.

Measure	White associations	Black associations	Asian associations	Character ratings
White associations				
Black associations	0.25 (0.07)			
Asian associations	0.01 (0.96)	–0.10 (0.46)		
Character ratings	0.33 (0.01)	0.04 (0.76)	0.05 (0.74)	
Attitudes toward blacks	0.10 (0.44)	0.01 (0.97)	0.02 (0.88)	0.24 (0.08)

Perhaps it is not surprising that exposure to prowhite nonverbal bias failed to increase self-reported racial prejudice; strong norms against racial prejudice may place a ceiling on self-reports of racial prejudice. Nonetheless, the results of study 4 suggest that exposure to nonverbal bias influenced (i) race associations, (ii) feelings toward particular white and black persons (television characters), and (iii) self-reported racial prejudice.

In conclusion, Americans are exposed, via television, to nonverbal race bias, and such exposure can influence perceivers' race associations and self-reported racial attitudes. Nonverbal behavior that communicates favoritism of one race over another can be so subtle that even across a large number of exposures, perceivers are unable to consciously identify the nonverbal pattern. Yet despite (or perhaps because of) this subtlety, exposure to nonverbal race bias may transmit race bias to perceivers.

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31. We thank H. Fitzgerald and S. Malahy for their Herculean efforts in data collection. The project described here was supported by National Institute of Mental Health Award no. F32MH078350 (M.W.) and National Institute of Health Award no. R01 MH070833-02 to (N.A.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health or the National Institutes of Health.

Supporting Online Material

www.sciencemag.org/cgi/content/full/326/5960/1711/DC1
Materials and Methods
SOM Text
Tables S1 to S5
References

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POSTDOCTORAL POSITION (100 percent, multiyear) in mouse genetics and neurodegenerative disease available immediately at University of California, Davis to use and generate mouse models to study the genetic, cellular, molecular, and mitochondrial mechanisms of neurodegenerative disease. Expertise in cloning, knockouts, and conditional gene expression as well as molecular and biochemical experience are required. Salary depends upon experience (NIH scale). Send curriculum vitae to **e-mail: gcortopassi@ucdavis.edu**. **Website: http://cortopassilab.ucdavis.edu/**. *UCD is an Affirmative Action/Equal Opportunity Employer.*

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To apply, please contact:

Xiangmin Xu, Ph.D.
Assistant Professor
Department of Anatomy & Neurobiology
School of Medicine
University of California, Irvine
Irvine CA 92697-1275
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BIOMATHEMATICS

The Department of Biological Sciences, University of Wisconsin-Milwaukee invites applicants for a faculty position in biomathematics at the **ASSISTANT** (tenure-track) or **ASSOCIATE PROFESSOR** level. We are seeking outstanding candidates with a Ph.D. in biology or a related area and with postdoctoral research experience. Applicants whose work has an aquatic focus, and with expertise in bioinformatics, genomics, computational genetics, ecological modeling, evolutionary biology, systems biology, or biological aspects of climate modeling, are preferred. The successful candidate will be expected to develop a vigorous, externally-funded research program, take an active role in directing undergraduate and graduate education, and contribute to teaching in biomathematics and core biology courses. This position is part of an interdisciplinary research initiative in aquatic biomathematics, involving biological and mathematical sciences and the UWM Great Lakes WATER Institute.

Potential applicants are encouraged to visit our **websites: www.biology.uwm.edu, www.math.uwm.edu,** and **www.glwi.uwm.edu.** To apply, please go to **www.jobs.uwm.edu/applicants/Central?quickFind=51144.** A completed application should include: cover letter, curriculum vitae, statement of research goals, statement of teaching interests, and three representative publications. Applicants should arrange to have three letters of professional reference sent as pdf attachments to the departmental chair **(e-mail: sandgren@uwm.edu)** or mailed to 'Biomathematics Search' at the following address: **Department of Biological Sciences, University of Wisconsin-Milwaukee, P.O. Box 413, Milwaukee, WI 53201.** Screening of candidates will begin January 18, 2010 and continue until the position is filled. Appointment begins August 2010. *University of Wisconsin-Milwaukee is an Equal Opportunity/Affirmative Action Employer.*

POSTDOCTORAL POSITIONS Cell Biology / Immunology

The Department of Medicine, Karolinska Institute, Stockholm, Sweden is seeking a **Postdoctoral Researcher**. The ultimate goal of the laboratory is to understand the underlying mechanisms of lymphocyte cytotoxicity, in part through the study of human immunodeficiency syndromes. Requirements include a Ph.D. in cell biology or immunology with less than three years of postdoctoral experience, outstanding microscopy or biochemical skills, publications in internationally renowned peer-reviewed journals, and good communication skills. Send curriculum vitae, names of three references, and a statement of research interests to **e-mail: yenan.bryceson@ki.se** or **hans-gustaf.ljunggren@ki.se**

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2009
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ANNE EICHMANN

The 2009 Liliane Bettencourt Prize for Life Sciences has been awarded to Anne Eichmann, PhD, currently director of an Inserm Unit at the Collège de France, Paris, in recognition for her achievements in the field of angiogenesis.

Anne Eichmann's group explores the molecular basis of the formation of blood and lymphatic vessels, and in particular the mechanisms that underlie the formation of the arterial tree. Understanding blood and lymphatic vessel formation is currently a subject of intense clinical interest because of the roles played by both types of vessel in cancer and ischemia. Anne's research has notably demonstrated that vessel growth shows anatomical and functional similarities to axon growth and guidance processes. Her earlier contributions are the cloning of receptors for vascular endothelial growth factor (VEGF) and demonstration of their endothelial cells specific expression, the isolation of the hemangioblast, a common precursor for endothelial and haematopoietic stem cells, and understanding of arterio-venous and lymphatic differentiation. Anne Eichmann's research is important at the fundamental biological but also translational, medical and therapeutic level.

The Liliane Bettencourt Prize for Life Sciences of € 250,000 is an essential part of the Bettencourt Schueller Foundation's commitment to Biomedical Research. It aims to support a top-level European researcher under the age of 45, along with his or her team, to pursue their work in the field of Life Science. The international Jury for the Award is chaired by Professor Pierre Corvol, Administrator of the Collège de France and member of the American Academy of Arts and Science and of the French Academy of Science.

The Bettencourt Schueller Foundation was created in 1987 by Mrs. Liliane Bettencourt, in memory of her father, the late Eugène Schueller, founder of L'Oréal. Its mission is to encourage entrepreneurship in Sciences, Arts and Social Commitment. The Foundation Bettencourt Schueller dedicates around 55 % of its total budget to finance scientific education and to directly support researchers.

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Washington University in St. Louis

Multiple Tenure-track/Tenured Faculty Positions

The Department of Computer Science and Engineering (CSE) and the School of Medicine (WUSM) are jointly searching for multiple tenure-track faculty members with outstanding records of computing research and a serious interest in collaborative research on problems related to biology and/or medicine. Appointments may be made wholly within CSE or jointly with the Departments of Medicine, Genetics, or Pathology and Immunology.

CSE and WUSM have a long-term strategic commitment to integrating computing and science. As part of that commitment, we expect to make synergistic hires with a combined research portfolio spanning the range from fundamental computer science/engineering to applied research focused on science or medicine. Specific areas of interest include, but are not limited to:

- Analysis of complex genetic, genomic, proteomic, and metabolomic datasets;
- Algorithms for statistical genetics including genome-wide association studies;
- Molecular systems biology and pathway/network modeling;
- Databases or data mining applied to medical records;
- Natural language processing with the potential for biomedical applications;
- Computer engineering with applications to medicine or the natural sciences;
- Wireless sensor networks with medical applications;
- Visualization with the potential for biomedical applications;
- Theory/Algorithms with the potential for biomedical applications;
- All areas of medical informatics, clinical or public-health informatics;
- All areas of computational biology and biomedical informatics

These positions will continue a successful, ongoing strategy of collaborative research between CSE and the School of Medicine, which is consistently ranked among the top 3 medical schools in the United States. CSE seeks to build on and complement its strengths in biological sequence analysis, biomedical image analysis, and biomedical applications of novel computing architectures.

Washington University is a private university with roughly 6,000 full-time undergraduates and 6,000 graduate students. It has one of the most attractive university campuses anywhere and is adjacent to one of the nation's largest urban parks, in the heart of a vibrant metropolitan area. St. Louis is a wonderful place to live, providing access to a wealth of cultural and entertainment opportunities without the everyday hassles of the largest cities.

We anticipate appointments at the rank of Assistant Professor; however, in the case of exceptionally qualified candidates appointments at any rank may be considered. Applicants must have a Ph.D. in computer science, computer engineering, electrical engineering, biomedical engineering, computational biology, biomedical informatics, statistical genetics, or a closely related quantitative field and a record of excellence in teaching and research appropriate to the appointment level. The selected candidate is expected to build an externally-supported research program, teach and mentor students at the graduate and undergraduate levels, and foster interdisciplinary interactions with colleagues throughout the university. Candidates who would contribute to enhancing diversity at the departmental and university levels are strongly encouraged to apply. Applications from academic couples are welcomed and encouraged.

Qualified applicants should submit a complete application (cover letter, curriculum vitae, research statement, teaching statement, and names of at least three references) electronically by following the directions provided at **http://cse-wusm-faculty-search.wustl.edu**. Other communications may be directed to **Prof. Michael Brent, Department of Computer Science and Engineering, Campus Box 1045, Washington University, One Brookings Drive, St. Louis, MO 63130-4899**.

Applications submitted before **January 31, 2010** will receive full consideration.

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Chinese Academy of Sciences
Max-Planck-Gesellschaft

The Chinese Academy of Sciences (CAS) and the Max-Planck-Gesellschaft (MPG)

are searching for a full-time department director for the

CAS – MPG PARTNER INSTITUTE FOR COMPUTATIONAL BIOLOGY (PICB) in Shanghai

Legally and administratively, the Partner Institute is an institute of the CAS, located on the CAS Campus of the Shanghai Institutes for Biological Sciences (SIBS).

The aim of this interdisciplinary and theoretically oriented Institute is to account for the increasing involvement of mathematical, computer science and engineering methods in modern biology and to allow for novel approaches of research at the interfaces between the pertinent disciplines (e.g., computational biology, genomics, systems biology, neurobiology, computational biophysics, biomolecular simulations).

We invite applications from scientists with an outstanding international research record who are willing to take full advantage of the unique challenge of leading the research at this interdisciplinary and theoretical/computational institute. The proximity to experimentally oriented, internationally competitive research institutes on the SIBS campus allows for close scientific cooperation and interaction between theoretical and experimental research. Strong collaboration with one or more Max Planck Institutes in Germany is encouraged and will be expressively documented and fostered by appointing him/her as a Fellow of MPG.

The recruitment and appointment procedure for the director position will be carried out jointly by CAS and MPG. The position will offer full scientific and economic independence comparable to that of a director/head of department at a Max Planck Institute.

The initial appointment will be for five years and can be extended after review by the Institute's internationally composed Scientific Advisory Board.

Qualified candidates should submit curriculum vitae, a short statement of research interests and scientific goals, and reprints of key publications. Candidates should be prepared to attend a symposium to be held March 28-31, 2010 in Shanghai and are asked to include topic and abstract for a possible presentation in the application package.

To ensure full consideration, please submit a hard copy of your application by **Jan 8, 2010** to

Jiayang Li (Vice President of CAS)
Chinese Academy of Sciences
52 Sanlihe Road
Beijing 100864
P.R. China

And PDF-files of your application to the contact persons in Munich and Shanghai:

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Department of Health and Human Services
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Warren Grant Magnuson Clinical Center
Tenure-Track Physician
Clinical Center/Radiology and Imaging Sciences

This position is jointly located in The Warren G. Magnuson Clinical Center, Radiology and Imaging Sciences (RAD&IS) Department (http://www.cc.nih.gov/drd/) on NIH's Bethesda campus and the National Institute of Allergy and Infectious Diseases (NIAID) Integrated Research Facility (IRF) at Fort Detrick in Frederick, Maryland. The tenure–track position, within the RAD&IS Center for Infectious Disease Imaging (CIDI), focuses on translational research applying diagnostic and molecular imaging to high-consequence infectious diseases. Research at the IRF is directed toward understanding host-pathogen interactions, discovering and elucidating mechanisms of action for medical treatments and developing targeted interventions for infectious diseases.

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Please submit your curriculum vitae, bibliography, and a letter describing your clinical, basic research, and management experience to: **Dr. Joseph Frank, Chair Tenure Track Search Committee, c/o Ms. Sondra Roberts-Jackson, NIH 10 Center Drive, Bldg. 10 Room B1N256, MSC 1074, Bethesda, Maryland 20892-1074. Email:Robertsjacksons@mail.nih.gov**.

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Selection for this position will be based solely on merit, without discrimination for non-merit reasons such as race, color, religion, sex, national origin, politics, marital status, sexual orientation, physical or mental handicap, age or membership or non-membership in an employee organization.

National Institute of Neurological Disorders and Stroke, NIH
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A staff scientist position is available to lead a newly formed Animal Model Unit that will be shared for projects by several investigators belonging to Stroke Branch (SB) and Neuroimmunology Branch (NIB). The emphasis is placed not only on technical expertise, but also on collaborative spirit and enthusiasm for translational work. It is expected that the staff scientist will be independent in developing and troubleshooting assays and supervising the technical staff and fellows, but that s/he will work closely with NIB and SB PIs in development of projects and ideas. The applicant should have experience with animal models of neuroinflammation and stroke (such as experimental autoimmune encephalomyelitis (EAE), and/or viral models of demyelinating diseases, middle cerebral artery occlusion, autologous clot model) and in vitro oxygen/glucose deprivation ("stroke-in-a-dish") models. Expertise and experience in MRI studies of animal stroke and neuroinflammation models (that provide an opportunity to link the combination of animal imaging and laboratory defined measures of cellular and molecular pathobiology with the combination of human imaging and biomarkers in parallel clinical trials), transgenic systems, and more advanced in-vitro cultures, such as organotypic cultures and immune cell/CNS tissue cell co-cultures are not necessary, but would be highly welcomed. Experience with any of the following techniques that are used in the associated labs: isolation of CNS infiltrating immune cells, phenotyping of immune cells by flow cytometry, mRNA isolation and analysis, analyses of soluble factors by ELISA, western blot, and molecular biology methods such as transfection and microRNA techniques, high throughput screens, or computer sciences to integrate and analyze genetic, molecular, physicochemical, functional and behavioral data would be viewed as added value.

Application instructions: Please send a letter describing your research interest and long-term goals, together with CV and names/contact information of 3 references to: **John M. Hallenbeck, M.D., Chief, Stroke Branch, NINDS, NIH, Bldg 10/Rm 5B02, 10 Center Drive MSC1401, Bethesda, MD 20892-1401, USAor to HallenbJ@ninds.nih.gov**. Applications will be received until **January 22, 2010**.

NIEHS
National Institute of Environmental Health Sciences
National Institutes of Health

Director, Division of Extramural Research and Training (DERT)
Research Triangle Park, NC

The National Institute of Environmental Health Sciences of the National Institutes of Health is seeking an exceptional candidate to fill the position of Director, Division of Extramural Research and Training (DERT). The incumbent of this position will direct the Institute's Extramural Research Program, which is organized into seven branches and centers and is composed of 56 FTEs (http://www.niehs.nih.gov/research/supported/dert/index.cfm). DERT is responsible for approximately 874 research grants, including those supported by the American Recovery and Reinvestment Act Funds (ARRA), for a total of $388 million. The Division supports environmental health sciences research, from basic mechanistic research to clinical studies, including children's health, breast cancer, Parkinson's and other neurodegenerative diseases, respiratory diseases and reproductive health, to name a few. The Division is developing the next generation of environmental scientists through training, fellowship, and career development programs.

The position of Director, DERT, is one of the top five senior level positions reporting directly to the Director, NIEHS and is part of the Institute's leadership team. The Director, DERT also serves as a principal advisor to the Institute Director on scientific affairs affecting the extramural community; develops and recommends procedures and policy for the execution of the research program; determines effectiveness of current programs and recommends new research programs in order to meet national environmental health needs. Additionally, the incumbent will develop collaborations and relationships with other Federal agencies, advocacy groups and industry.

Candidates must have an M.D., Ph.D. or a doctoral degree in a discipline relevant to environmental health sciences and have a strong publication record. Applicants should be aware of current trends, research directions and needs in environmental health sciences and be conversant with the policy implications of the research. Candidates should have a proven track record of administrative experience and scientific program development. Familiarity with NIH procedures and programs is preferred. Adherence to NIH ethics policies is required. This is a Title 42 appointment and salary will be commensurate with level of experience.

Interested persons should submit curriculum vitae, contact information for 3 people to provide a reference, a statement regarding reasons for interest in the position and unique qualifications by **February 27, 2010** to: Ms. Stephanie Jones, NIEHS, Office of Human Resources, P.O. Box 12233, Mail-drop K1-1, Research Triangle Park, NC 27709 or Dert_Director_Recruit@niehs.nih.gov, Vacancy: NIEHS-10-DERT.

Please send questions regarding the position to:
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e-mail: croyler@mail.nih.gov.

Please send questions regarding the Institute/Division to:
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National Institutes of Health

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UTMB
The University of Texas Medical Branch

Faculty Position in Mouse Genetics
Job Opening #20192

The Department of Biochemistry and Molecular Biology and the George P. and Cynthia Woods Mitchell Center for Neurodegenerative Diseases, in collaboration with the Department of Neuroscience and Cell Biology at The University of Texas Medical Branch at Galveston (UTMB), seek an outstanding candidate for a tenure-track faculty position at the Associate Professor or Full Professor level. The ideal candidate will have an established, extramurally funded program in the biological sciences with a strong focus in mouse genetics with a track record in neurogenetics or cancer genetics. The successful applicant will have opportunities for interactions with centers of scientific excellence in aging, cancer, structural biology and/or addiction research. An attractive recruitment package of salary, start-up funds and equipment, as well as research space will be offered commensurate with the applicant's qualifications.

Interested applicants should refer to job **ID 20192** and submit a curriculum vitae, a summary of research accomplishments and future goals (3-5 pages), as well as contact information of five references to:

George R. Jackson, MD, PhD
Professor and Director
Mouse Genetics Search Committee
George P. and Cynthia Woods Mitchell
Center for Neurodegenerative Diseases
The University of Texas Medical Branch,
301 University Blvd.,
Galveston, Texas 77555-1045

Faculty Position in Mass Spectrometry
Job Opening #20282

The Sealy Centers for Molecular Medicine (SCMM) and for Cancer Cell Biology and the Department of Biochemistry and Molecular Biology at the University of Texas Medical Branch at Galveston (UTMB) are seeking an outstanding candidate for a tenured track faculty position at the Associate or Professor level. The ideal candidate will have an established program in the biological sciences with a strong focus in mass spectrometry. Areas of special interest at UTMB are proteomic studies, including post-translational modifications, biomarker development, high-throughput approaches, as examples, and mass spectrometry applications development for proteomics. The successful applicant will be jointly appointed in the NHLBI Proteomics Center focusing on airway inflammation, the NIAID Clinical Proteomics Center and the Institute for Translational Sciences. Additional opportunities exist for interactions with centers of scientific excellence in aging, infectious diseases, environmental health, neurodegenerative diseases and/or addiction research.

UTMB houses strong research core services including bioinformatics/computational biology, organic synthesis, molecular biology, x-ray crystallography, NMR, and biophysical solution chemistry. The Mass Spectrometry Core has three Ph.D. trained mass spectrometrists and four high end MALDI/TOF/TOF and LC/MS/MS instruments including a ThermoFisher Orbitrap Velos.

An attractive recruitment package of salary, start-up equipment, newly renovated space, and junior faculty positions will be offered commensurate with the applicant's qualifications. Interested applicants should refer to job **ID 20282** and submit a curriculum vitae, a summary of research accomplishments and future goals (3-5 pages), as well as contact information of five references to: **Allan R. Brasier, MD, Professor and Director, Sealy Center for Molecular Medicine, University of Texas Medical Branch, 8.128 Medical Research Building, Galveston, TX 77555-1055.**

The University of Texas Medical Branch at Galveston is an Equal Opportunity, Affirmative Action Institution which proudly values diversity. Candidates of all backgrounds are encouraged to apply.

Senior Research Positions at Swedish Universities

The Swedish Research Council announces Senior Research Positions within natural and engineering sciences. The positions are intended for scientists who have obtained a Ph.D., where the date of exam, with a few exceptions, is not older than ten years prior to the end of the application period. The primary obligation of Senior Research Position appointees is to conduct research. The positions are financed for a maximum of six years.

There is normally one position each within the following 11 areas:

- Analytical chemistry for a sustainable development
- Bioinformatics
- Biomedical engineering
- Eukaryotic molecular cellbiology
- Experimental studies of dynamic processes involving atoms, molecules and clusters
- Optimization of antenna systems
- Parallel computation methods and architectures
- Particle astrophysics
- Photoinduced control of molecular and material functions
- Polar oceanography
- Semiconductor physics, electronics, electrical engineering and photonics

The proposal must be approved by a Swedish host university or other Swedish host higher education institution.

Apply at www.vr.se no later than February 18, 2010
Application form and instructions can be found at www.vr.se/english in late December.

Vetenskapsrådet

UNIVERSITY of NEW HAMPSHIRE

Seven Tenure Track Faculty Positions in
Sustainable Agriculture and Ecosystem Science

The University of New Hampshire seeks outstanding applicants for seven new faculty positions in the areas of sustainable agriculture and sustainable ecosystem science and management. Successful candidates will be expected to develop a strong research and teaching program in one of the following areas:

- Agroecology/Forage Crops
- Applied Forest Ecology
- Aquatic Biogeochemistry
- Landscape Ecology
- Plant Pathology/Plant Microbe Interactions
- Soil Fertility and Biogeochemistry
- Specialty Crop Improvement

Applicants must have a Ph.D. in a relevant field. Preference will be given to those candidates displaying an interest and ability in working across traditional disciplinary/departmental boundaries. It is anticipated that these positions will be filled at the Assistant Professor level. These positions will be located within the College of Life Sciences and Agriculture (COLSA) and successful candidates will be matched with the department that best suits their interests and expertise. The University actively creates and nurtures a dynamic learning environment in which qualified individuals of differing perspectives, life experiences and cultural backgrounds pursue goals with mutual respect and a shared spirit of inquiry. These new faculty are expected to establish vibrant, collaborative research programs, and to enhance the university's prominence in interdisciplinary research, undergraduate and graduate teaching, and outreach. UNH is a Research-I, Land, Sea and Space Grant University that has been recognized both nationally and internationally for research excellence and a commitment to sustainability and public engagement.

Application Process: Information, including detailed position descriptions, are available at **http://www.colsa.unh.edu/employment/**. All applicants will be required to apply online at **https://jobs.usnh.edu**. Review of applications will begin on January 15, 2010 and will continue until the positions are filled.

The University actively seeks excellence through diversity among its administrators, faculty, staff and students and prohibits discrimination on the basis of race, color, religion, sex, age, national origin, sexual orientation, gender identity or expression, disability, veteran status, or marital status. Application by members of all underrepresented groups is encouraged.

Klaas Heinemann wants to make the world a better place – for everyone. As a physician at Bayer, Klaas knows he is doing just that. Searching for solutions and never giving up. That is the passion that unites all of us at Bayer. We call it the Bayer Spirit. If you feel it, too, then it is high time we had a chance to talk about a career at Bayer.

Lab Head, Cardiovascular in vivo Target Validation

Job description As a Laboratory Head of "Cardiovascular in vivo Target Validation" you will be responsible for leading and supervising an in vivo cardiovascular pharmacology lab at the Pharma Research Center in Wuppertal, Germany. You will manage and implement a variety of animal models for the company's drug discovery programs to support in vivo target validation. You will oversee the performance and scheduling of animal experiments in the field of e.g. pulmonary hypertension, heart failure, cardio/renal protection, atrial fibrillation, thrombosis, peripheral artery occlusive disease, acute lung injury or sepsis. In addition, you will have the responsibility for creating novel ideas for drug targets and develop a patho- physiological understanding how modulation of the target can improve disease. Validation of these targets in animal models using either tool compounds or genetically engineered animals is one of the key tasks. Furthermore, you will also ensure the development of novel animal models matching the clinical situation in humans. In particular you will ensure the supervision of cooperations with clinics/hospitals, CRO's in the field of cardiovascular animal models and the collection of clinic samples.

Your qualifications You have a PhD or MD degree in biology, medicine, veterinary medicine or pharmacy with several years experience in various cardiovascular animal models. Postdoctorial experience or industrial background would be a plus. A background in validation of biological protein targets would be an asset. Moreover, you have a mature, self-confident and well-balanced personality and possess a high standard of ethical and intellectual integrity. Beyond that you have a strong leadership style and a stable personality, possessing social competence and distinct management abilities. Further, you have profound knowledge of the German and English language. The ability to supervise, coach and mentor your team and have a track record of effective project contribution is required.

Your application We offer a competitive salary and benefits package and will support individual as well as professional development. If you think that you have the right qualifications and wish to be part of our team, please apply online at www.myBayerjob.de, regarding the Reference Code 0000008051, along with enclosures such as your cover letter, CV and references.

www.myBayerjob.com **Phone +49 214 30 9 97 79**

ENGINEERING OF ADVANCED MATERIALS

The Friedrich-Alexander-Universität Erlangen-Nürnberg with its 26,000 students and 12,000 employees is one of the leading European Research Universities with a strong focus on engineering, natural sciences and medicine. The university is committed to excellent research and interdisciplinary academic education.

The research cluster of excellence "Engineering of Advanced Materials – Hierarchical Structure Formation for Functional Devices" is supported by the German Excellence Initiative and focuses on the science and engineering of hierarchical materials organised from the molecular to the macroscopic levels and the related process technologies. Based on a coherent methodological approach the following research areas are explored:

- **Cross-cutting topics: Particle technology, nanomaterial characterization and multiscale modelling and simulation**
- **engineering of nanoelectronic materials**
- **engineering of photonic and optic materials**
- **engineering of catalytic materials**
- **engineering of lightweight materials**

The vision of the cluster is to bridge the gap between fundamental research and real-world applications of modern high-performance materials in key scientific and engineering areas.

In order to attract outstanding middle career scientists the cluster of excellence invites applications for an

Erlangen Excellence in Engineering Materials Award (W2, tenure track)

The Award consists of a W2-professorship for 4 years and flexible resources of up to 750,000 € for independent, interdisciplinary, and fundamental research of the awardee's own choice, but in cooperation with the cluster. The successful candidate is expected to develop an internationally recognized fundamental research program strongly interlinked with the cluster's research areas. Applicants are asked to submit a proposal (maximum 5 pages) that clearly expresses their excellence in research and their collaborative research plans within the cluster.

The Award addresses itself to candidates with an excellent track record in at least one of the mentioned research areas. Applicants should be exceptional researchers with outstanding university undergraduate and doctoral degrees in natural sciences or engineering as well as excellent teaching skills, and a habilitation or equivalent other qualification, which may have been gained outside university or within a "Junior Professorship".

The appointment is for four years initially with the possibility of a permanent position, following a positive evaluation (tenure track).

The Universität Erlangen-Nürnberg actively encourages applications from female candidates in an effort to increase female representation in research and teaching.

Given equal suitability for the appointment the applications of disabled candidates will be given priority.

The position is available immediately.

Application documents (curriculum vitae, photograph, copies of degree certificates and a selection of the most important publications) and a proposal (not more than 5 pages) must be submitted before **2010-01-15** by e-mail to

Friedrich-Alexander-Universität Erlangen-Nürnberg
Exzellenzcluster Engineering of Advanced Materials
Prof. Dr.-Ing. Wolfgang Peukert
Nägelsbachstrasse 49 B, D-91052 Erlangen
e-mail: administration@eam.uni-erlangen.de
www.eam.uni-erlangen.de

Friedrich-Alexander-Universität Erlangen-Nürnberg

www.uni-erlangen.de

Massachusetts Institute of Technology

Come work with us!

Faculty Position in Biological Technologies

Department of Biological Engineering

The MIT Department of Biological Engineering invites applications for a tenure-track faculty position at the assistant professor level, to begin July 2010 or thereafter. Applicants should hold a Ph.D. in a science or engineering discipline related to biological engineering. A more senior faculty appointment may be considered in special cases. The candidate is expected to direct a pioneering research program that develops and applies transformative biological technologies in critical areas such as energy, the environment, nutrition, or novel materials. Faculty duties also include teaching at the graduate and undergraduate levels, and supervision of student research.

We especially encourage individuals from underrepresented groups to apply, because of MIT's strong commitment to diversity in engineering education, research and practice.

Interested candidates should send application materials to the Biological Engineering Faculty Search Committee at: **be-fac-search1@mit.edu**. Each application should include: a curriculum vitae; the names and addresses of three or more references; a strategic statement of research interests; and a statement of teaching interests specifically in the context of the Biological Engineering graduate and undergraduate educational programs at MIT (http://web.mit.edu/be/education/ and http://web.mit.edu/be/education/ugrad.htm). We request that each candidate arrange for the reference letters to be sent directly to **be-fac-search1@mit.edu**.

Questions may be directed to: Prof. Douglas Lauffenburger, Head, Department of Biological Engineering, MIT 16-343, 77 Massachusetts Avenue, Cambridge, MA 02139 or lauffen@mit.edu.

Responses by 1 February 2010 will be given priority.

MIT is an Equal Opportunity/Affirmative Action employer.

http://web.mit.edu

LSU
LOUISIANA STATE UNIVERSITY

ASSISTANT PROFESSOR (Computational Biologist/ Two positions)-Department of Biological Sciences

ASSISTANT/ASSOCIATE/FULL PROFESSOR (Computational Biologist)

Louisiana State University invites applications for three faculty positions in Computational Biology, broadly defined. **Required Qualifications: (All positions)** Ph.D. or equivalent degree; successful track record of productive research; **(Asst Prof)** A.B.D. candidates considered, with Ph.D. by May 2010. **Additional Qualifications Desired: (All positions)** A computational biologist who investigates fundamental biochemical, cellular, developmental or evolutionary questions; areas of interest should include, but are not limited to: biomolecular dynamics and structure-based drug design, proteomics, bioinformatics, systems biology and interaction networks, metabolomics, evolutionary genomics, and metagenomics analyses. **Responsibilities: (All positions)** establishes a vigorous, extramurally funded research program; contributes to undergraduate and graduate teaching; contributes to the development of a center of excellence in Computational Biology at LSU. The Assistant/Associate/Full Professor will work closely with faculty in Biological Sciences and other departments at LSU, as well as the CCT faculty to foster the development of a center of excellence in Computational Biology at LSU. The CCT **(http://www.cct.lsu.edu/home)** offers an innovative and interdisciplinary research environment for advancing computational sciences, including a highly competitive computing environment with access to 100 TFlops of computing resources in conjunction with the Louisiana Optical Network Initiative (LONI). The LONI Institute **(http://institute.loni.org/)** is a bold new inter-university collaboration aiming to fill a dozen new faculty positions in related areas. LSU is part of the national TeraGrid. For additional information visit our departmental website: **http://www.biology.lsu.edu**. Rank and salary will be commensurate with qualifications and/or experience. We encourage applications from women and minorities. An offer of employment is contingent on a satisfactory pre-employment background check. Application deadline is January 29, 2010 or until candidates are selected.

Apply online at: www.lsusystemcareers.lsu.edu.
Asst. Prof. #034191 and Asst./Assoc./Full Prof. #034190.

LSU SYSTEM IS AN EQUAL OPPORTUNITY/EQUAL ACCESS EMPLOYER

RUTGERS
UNIVERSITY

Energy Research Initiative

Faculty Positions – Meeting the Challenges for New Jersey and the Nation

The Rutgers Energy Institute (REI), in conjunction with the School of Engineering, School of Arts and Sciences, School of Environmental and Biological Sciences, and Edward J. Bloustein School of Planning and Public Policy, has tenure-track faculty openings in energy-related science technology, engineering, economics, and public policy. Except as noted, preference will be given to entry-level assistant professors; however, exceptional applicants at the senior level will be considered. Special consideration will be given to faculty who bridge one or more disciplines. The REI can facilitate appointments between schools as appropriate.

Except as noted preference will be given to entry-level assistant professors; however, exceptional applicants at the senior level will be considered. Special consideration will be given to faculty who bridge one or more disciplines. The REI can facilitate appointments between schools, as appropriate.

Candidates should supply a detailed CV, a brief statement of research interests and goals, and letters from three references. These positions will remain open until the best candidates are identified; however, applications received by January 15, 2010, will be given priority in the initial selection process.

RUTGERS
Energy Institute

Rutgers, The State University of New Jersey
Rutgers Energy Institute
http://rei.rutgers.edu

Rutgers University is an Equal Opportunity/Affirmative Action Employer.

School of Engineering http://www.soe.rutgers.edu

The seven departments of the Rutgers School of Engineering are embarking on a hiring thrust in the broad area of Energy. The following areas are of particular interest:

- Professor in Power Engineering: including large-scale power generation, storage and distribution.
- Professor in Renewable Energy: focused on cutting-edge research on energy efficiency, novel energy sources, and energy life cycles.
- Professor in Energy Storage: with research emphasis on novel electrical storage strategies and pathways.
- Professor in Energy Harvesting: including photoelectric energy conversion and novel photovoltaic catalysis/artificial photosynthesis.
- Professor in Nuclear Engineering: with interest in reactor design and safety/next generation of nuclear power.

Contact: D. P. Birnie, III, energy@soemail.rutgers.edu

School of Arts and Sciences http://sas.rutgers.edu
School of Business http://business.rutgers.edu

- Professor in Business and Natural Resources: Joint hire with the Department of Earth and Planetary Sciences and the School of Business to fill an endowed chair at the level of Full Professor. Successful candidate should have broad knowledge of geosciences, relating to energy and climate as well as an understanding of relevant economic and business policies. A Ph.D. in Geosciences or Economics with complementary experience is required; experience with energy valuation models is desired.

Contact: reisearch@sas.rutgers.edu

School of Arts and Sciences http://sas.rutgers.edu

- Professorships in Basic Energy Research: research can be in any area of energy, with a preference for alternative energy, novel energy materials, photovoltaics, catalysis, thermoelectrics, batteries, fuel cells, hydrogen generation and storage, and carbon capture. We are especially interested in hiring interdisciplinary scientists.

Contact: K. Fowler, kmfowler@rci.rutgers.edu

School of Environmental and Biological Sciences http://sebs.rutgers.edu

- Professor in Bioenergy Technology: Associate/Full Professor to conduct research and build a nationally recognized program in applied waste-based/agriculture-based bioenergy technology. Will have Extension and outreach responsibilities and also serve as Director of the Rutgers EcoComplex.
- Professor in Energy Economics: Must be familiar with energy policy and related environmental and climate-change debates at the local and global levels. Expertise in any field of economics will be considered, provided research is relevant to public decision-making on sustainable energy. Knowledge of biofuels desirable.
- Professor in Energy Processes and Technologies: Conduct research in novel biological/chemical processes related to bioenergy or alternative energy systems. Specific areas of interest include bioelectricity and microbial fuel cells, biohydrogen and biomethane production systems, novel (bio) fuels, novel generation systems and distributed energy systems.

Contact: M. Brennan-Tonetta, Brennan@aesop.rutgers.edu

Edward J. Bloustein School of Planning and Public Policy (EJBSPPP) http://policy.rutgers.edu

- The EJBSPPP welcomes affiliations for those with an energy policy and economics focus to integrate with or bridge with other departments/research promoting national sustainable-energy strategies. The Center for Energy, Economic and Environmental Policy examines energy policies and technologies (http://policy.rutgers.edu/centers/ceeep.php); the Center for Green Building promotes green building through research, advocacy and education (http://policy.rutgers.edu/centers/green.php); and the EJBSPPP has long-standing research on nuclear energy, nuclear waste management, and alternative fuel sources.

Contact: J.W. Hughes, jwhughes@rutgers.edu

The European Commission is looking to recruit a

Principal Adviser

for the Research Directorate-General from the EU Member States (COM/2009/10222)

Director Designate of the European Research Council Executive Agency (ERCEA) in Brussels

The European Research Council Executive Agency (ERCEA), which is a component of the European Research Council (ERC), is a newly established Agency, dedicated to the promotion of frontier research. The ERCEA works in conjunction with the ERC Scientific Council, which is responsible for establishing the scientific strategy.

As other executive agencies, the ERCEA is in charge of the implementation of Community programmes and is managed by an Official of the European Communities seconded to the Agency as Director.

ERCEA is in particular responsible for all aspects of administrative implementation and execution of the "Ideas" specific programme, which forms part of the FP7 (Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007-2013)) and supports investigator-driven frontier research carried out across all fields by individual national or transnational teams in competition at the European level. The projects are proposed by individual investigators and funded at the European level, by the sole criterion of excellence: of the proposer ("Principal Investigator") and the project. The projects are evaluated by international panels of experts, who are selected by the planning and strategy component of the ERC, the Scientific Council.

ERCEA supports the work of the ERC Scientific Council, implements the evaluation and selection procedures, organizes peer reviews according to the principles established by the Scientific Council and ensures the proper financial and scientific management of the grants.

The ERCEA is located in Brussels and is expected, subject to the evaluation of its operations every 3 years, to manage the specific programme at least until 2017.

By 2013, ERCEA would have a staff complement of 389 and manage an operational budget of € 1,679 millions.

We look for a distinguished scientist with robust administrative experience.

Applicants should have: high level qualifications (PhD or equivalent experience) in any field of science or scholarship and very strong professional record in any field of fundamental research; knowledge of policy and practice relevant to scientific and technological research and experience of leadership in this area; excellent understanding of the challenges at stake in relation with frontier research; experience of budgetary, financial and human resources management in a national, European and/or international context; capacity to develop and manage a large agency, both at strategic and internal management level; ability to lead and motivate a large team in a European, multicultural and multilingual environment; understanding of the EU Institutions, their functioning and interaction as well as EU policies and international activities of relevance to the activities of the Agency; ability to communicate to the public and cooperate with stakeholders (European, International, National and Local Authorities, international organisations, etc); excellent written and oral communication and negotiation skills; in particular, excellent knowledge of English.

A full job description, selection criteria and application details can be found in the Official Journal C 295 A of 4 December 2009 or on the EUROPA website:
http://ec.europa.eu/dgs/personnel_administration/working_senior_mgt_en.htm

If you want to apply, you must register via the Internet by going to the website:
https://ec.europa.eu/dgs/personnel_administration/seniormanagementvacancies/CV_Encadext/index.cfm

The closing date for application is 5 March 2010.

On-line application will not be possible after 12.00 noon Brussels time.

http://ec.europa.eu

EUROPEAN COMMISSION

DES MOINES UNIVERSITY

Des Moines University is currently seeking applications from qualified candidates for a tenured or non-tenured **Anatomy Faculty position**. The successful candidate must possess a doctoral degree or be in the terminal stages of doctoral candidacy. Prior teaching experience in the anatomical sciences is strongly desired. In addition, candidates should have current and permanent legal rights to work in the U.S. and excellent communication, presentation and interpersonal skills. This individual will take part in our team-taught and broad-based anatomical sciences curriculum for medical, allied health and anatomy graduate students. The successful candidate is expected to pursue independent research leading to extramural funding and publications in advanced teaching innovations and/or other pertinent anatomic investigations.

The mission of our Anatomy department is to engage future health care providers, educators, scientists and community members in a dynamic, evidence-based discipline that fosters a professional environment of scholarly activity and service. Des Moines University takes great pride in the depth and breadth of its anatomy programs and its recent investment in new, digitally-equipped dissection laboratory facilities.

Des Moines is a vibrant, mid-size city with nationally recognized schools, low cost of living and many cultural activities and its location affords opportunity for scholarly collaboration with various Midwest universities and private institutions.

Persons interested in this position should submit their CV, contact information for three references, and a summary statement regarding their teaching philosophy, scholarly activities and goals using the online applicant tracking system located at **http://www.dmu.edu/employment**. Review of applications will begin immediately and continue until the position is filled. Candidates with questions specific to this position may also contact **Dr. M. Khan** at **515-271-1694** or email at **M.Khan@dmu.edu**. Des Moines University offers a competitive compensation package, including bonus, for this position. For a complete job description, faculty benefits or for more information on Des Moines University and its various academic programs, please visit **www.dmu.edu**.

Des Moines University is an EOE Employer.

Ecological Modeler
University of Maine

The School of Biology and Ecology and the Senator George J. Mitchell Center for Environmental and Watershed Research at the University of Maine invite applications for a tenure-track faculty position in **ecological modeling** at the Assistant or Associate Professor level to begin September 2010. The successful candidate will join a new Sustainability Solutions Initiative (SS1), an innovative program in sustainability science funded by a 5-year, $20 million NSF EPSCoR grant. The University has committed to continue this position as a regular faculty position at the grant completion. The successful candidate will participate in interdisciplinary research of coupled social-ecological systems and will work closely with a range of biological, physical and social scientists to develop and implement models in this area.

We seek an ecological modeler working at the population, community and/or ecosystem level, particularly someone who focuses on terrestrial-aquatic linkages. Preference will be given to candidates who conduct mechanistic modeling of ecological systems at regional and local scales, and who address questions related to terrestrial and aquatic processes and/or climate change. This is an academic year, tenure-track, 75% research/25% teaching position. Teaching is expected to include a graduate level course in the candidate's area of expertise, as well as an upper-level undergraduate ecology course. The successful candidate also will be expected to develop an internationally recognized research program, train graduate students, and actively engage in service to the profession, the university and the state of Maine. A Ph.D. is required in a relevant area of ecological sciences. Postdoctoral experience and prior success in high-quality publication and obtaining funding are desirable. Candidates at the Associate Professor level must have a proven track record of publication, external funding, graduate training, and teaching.

To apply, submit a resume, three letters of reference, and statements of teaching and research interests. Please send materials in PDF form to **SBE@umit.maine.edu** or in hard copy to: **Chair, Ecological Modeler Search Committee, School of Biology and Ecology, 5751 Murray Hall, University of Maine, Orono, ME, 04469**. Review of applications will begin **January 20, 2010** and will continue until the position is filled.

The University of Maine is an Equal Opportunity/Affirmative Action Employer committed to maintaining an intellectually and culturally diverse faculty.

Chief Scientists to head new laboratories
Permanent Position RIKEN, Japan

RIKEN invites applications for the position of Chief Scientists to lead new laboratories in the following areas:

RIKEN SPring-8 Center (RSC) has been playing a central role in the frontiers of science and technology from the materials to the life science fields by providing state-of-the-art experimental facilities utilizing brilliant light sources as well as by promoting its own research activities. The Innovative Light Sources Division, RSC has now an initiative for SPring-8 synchrotron source upgrade known as SPring-8 II. The successful candidate will be in charge of 1) leading and achieving the long-term project, "SPring-8 II 2019", which shall give birth to the 'ultimate' storage ring by the end of 2019, 2) promoting the international collaboration with the synchrotron radiation (SR) facilities all over the world as a research leader of accelerator physics in photon science. Applicants should have the ability and experience equivalent to that of a project leader at a SR facility and appropriate research experience supported by a distinguished research record and the ability to play a pivotal role in the research area over the long-term.

Conditions
The post is a permanent appointment, subject to RIKEN's mandatory retirement age of 60. Terms and conditions of employment shall include a director-level salary and be in accordance with RIKEN's procedures for appointing Chief Scientists.

Deadline and documents to be submitted
Applicants should send a full curriculum vitae and photograph; one copy each of five key publications; a statement (five sides of A4) explaining former research experience, reasons for their applications and proposals for research at RIKEN, and; the names and addresses of three referees. All documents should reach RIKEN by **31 March 2010**.

Applicants should address all correspondence to:
Dr. Masaki Takata, Head of the Chief Scientist Nominating Committee, Structural Materials Science Laboratory, RIKEN SPring-8 Center, RIKEN Harima Institute, Koto 1-1-1, Sayo-cho, Sayo, Hyougo 679-5148 JAPAN
(Tel: +81(0)791582942, e-mail:takatama@spring8.or.jp)

Further details: **http://www.riken.jp/engn/r-world/info/recruit/k100331_e_rsc.html**

The **Advanced Science Institute (ASI) at RIKEN** is applying its integrated and interdisciplinary resources to developing new research fields directed at solving global environmental and energy issues. To this end, ASI is planning to establish a laboratory that will work on developing new substances and materials or finding new functions for various substances and materials. To head this new laboratory as Chief Scientist, ASI seeks an individual who will be capable of implementing original environmental and energy research strategies over the medium and long terms, and who can pioneer new directions of research cutting across different research fields. Applicants should have appropriate research experience supported by relevant publications.

Conditions
The post is a permanent appointment, subject to RIKEN's mandatory retirement age of 60. However, it is possible, depending on evaluation results, to continue research after the age of 60 (73 maximum) as a Distinguished Senior Scientist. Terms and conditions of employment shall include a director-level salary and be in accordance with RIKEN's procedures for appointing Chief Scientists.

Deadline and documents to be submitted
Applicants should send a full curriculum vitae and photograph; list of publications; one copy each of five key publications; a statement (about five pages A4 sized paper) explaining former research experience and proposals for research at RIKEN; and the names and addresses of three referees. All applications should reach RIKEN by **April 30, 2010**.

Applicants should address all correspondence to:
Dr. Mizuo Maeda, Head of the Chief Scientist Nominating Committee, Bioengineering Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama, 351-0198 JAPAN
(Tel: +81(0)484679312, e-mail: mizuo@riken.jp)

Further details: **http://www.riken.jp/engn/r-world/info/recruit/k110430_e_asi.html**

Applications from overseas applicants are welcome. The successful candidate will be responsible for the laboratory's overall management and research strategy, directing research projects and contributing to more general aspects of RIKEN's management and research planning activities. RIKEN expects that the successful applicant will be able to take up this position on **October 1, 2010**.

Information about RIKEN is available on the RIKEN website: **http://www.riken.jp/**

Research for the Environment

HELMHOLTZ CENTRE FOR ENVIRONMENTAL RESEARCH – UFZ

The Helmholtz Centre for Environmental Research – UFZ is a research institution within the Helmholtz Association. It provides scientific contributions to the safeguarding of the natural basis of life and of human development potentialities for current and future generations under the challenges of global and climate change. In this way the UFZ contributes towards a sustainable development.

The Department of Ecological Modelling invites applications for

one Research Scientist position (m/f, full time)

three PhD-positions (or alternatively half-time PostDoc positions) (m/f)

within the framework of an "European Research Council Advanced Researcher Grant" for the project "Towards a Unified Spatial Theory of Biodiversity". The positions will start earliest on 1st February 2010 and the candidates will be recruited for three years.

Objective: The objective of the ERC project is to understand the relative importance of processes and factors that govern the composition and dynamics of species-rich communities. The project relies on data sets of large mega-plots of tropical forests and forest simulation models. Important parts of the project are quantification of the highly complex spatial structures found in these forests and their comparison with the output of forest simulation models.

A) PhD-position

will focus on process- and individual-based dynamic models for forests. Expertise in dynamic simulation models and excellent programming capabilities are required.

B) PhD-position

will focus on highly aggregated vegetation modelling approaches based on Markov chains and cellular automata (Hubbell-approach). Expertise in dynamic modelling and excellent programming capabilities are required.

C) PhD-position

will focus on quantification of complex spatial patterns and their relationship with species properties. A strong background in statistics and willingness to learn methods of spatial point pattern analysis and point process modelling are required.

D) Research Scientist position

The successful candidate will coordinate the spatial pattern analysis part of the ERC project and conduct challenging spatial analyses. A PhD, strong background in spatial statistics and point process modelling, and a strong international publication record are required.

Requirements: We are seeking for ambitious, highly motivated and team oriented scientists with keen interests in interdisciplinary research and conceptual issues in ecology. Applicants should have a degree and a solid background in Physics, Ecology or Applied Mathematics (or a related discipline), good knowledge of a modern programming language (e.g. Pascal, C++) and good skills in English (speaking and writing). Experience in ecological modelling is beneficial.

The place of work is Leipzig, Germany. Salary for positions A-C will be according to the appropriate civil service level (TVöD), Entgeltgruppe 13 (50%) and for position D according to the personal preconditions up to Entgeltgruppe 14 (TVöD). Women are explicitly encouraged to apply to increase their share in science and research. Physically handicapped persons will be favored if they are equally qualified.

For more detailed information, please, contact:

Positions A, B: Dr. habil. Andreas Huth, Phone: +49 341 235-1719; andeas.huth@ufz.de

Positions C, D: Dr. habil. Thorsten Wiegand, Phone: +49 341 235-1714; thorsten.wiegand@ufz.de, http://www.thorsten-wiegand.de/towi_ERC.html

Please send your complete application documents until **8. 1. 2010** under the code digit **101/2009** to the personnel department, P.O. Box 500136, D-04301 Leipzig, Germany or by e-mail to application@ufz.de. Applications are taken until the position is filled.

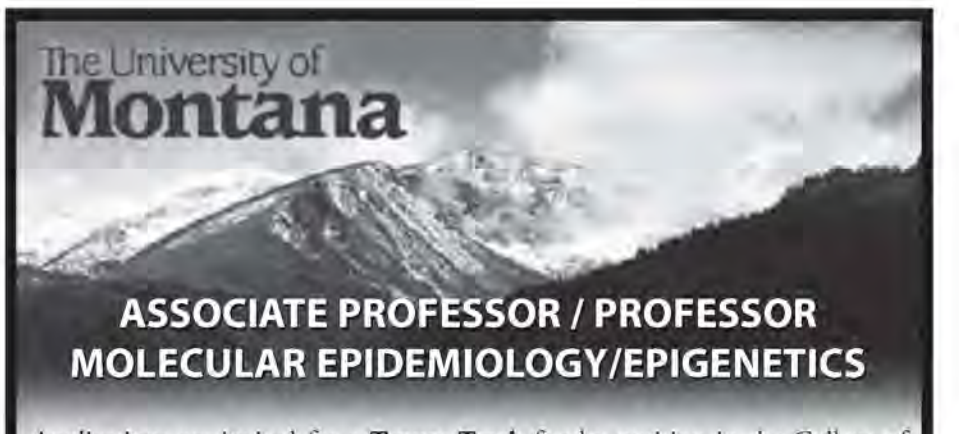
WASHINGTON STATE UNIVERSITY

World Class. Face to Face.

Full-Time Tenure Track Faculty Position in Zoonotic Infectious Diseases

The mission of the Washington State University School for Global Animal Health is to improve human health by control of infectious diseases at the animal-human interface (**http://www.globalhealth.wsu.edu**). Founded by a gift from the Bill and Melinda Gates Foundation, the School is expanding and seeks an outstanding individual for a 12-month, tenure-track position in research and graduate/post-doctoral education at our Pullman Campus. The successful applicant will be expected to develop and implement an innovative, productive, and extramurally funded laboratory and/or field-based research program that addresses zoonotic infectious diseases. Research and graduate education in the School, supported by NIH, USDA, and the Wellcome Trust, are focused on animal infectious diseases, including both zoonotic pathogens and pathogens that constrain livestock development in resource-poor countries. In addition to current modern research facilities, the School is presently constructing a new BSL2/3 research building funded by the Gates Foundation and the State of Washington. A doctoral degree (DVM, MDor PhD), and post-doctoral research experience (post-DVM, post-MDor post-PhD) is required. A demonstrated potential for successful acquisition of extramural funding, demonstrated publication in high impact international journals, and current or projected research relevant to the mission of the School for Global Animal Health are preferred. The appointment may be as an Assistant or Associate Professor, depending on experience and record of achievement. The successful candidate will be expected to work closely with faculty to further develop the School's graduate program and to demonstrate a commitment to the School's public health and humanitarian mission. Review of applications will begin on **February 1, 2010**. Submit letter of application, curriculum vitae, and names and addresses of three references to: **Dr. Wendy Brown, Search Committee Chair, c/o Ms. Jill Griffin, School for Global Animal Health, Washington State University, P.O. Box 647040, Pullman, WA 99164-7040.**

WSU is an EEO/AA Employer. Protected group members are encouraged to apply. For more information: ***http://www.vetmed.wsu.edu/employment/.***



ASSOCIATE PROFESSOR / PROFESSOR MOLECULAR EPIDEMIOLOGY/EPIGENETICS

Applications are invited for a **Tenure-Track** faculty position in the College of Health Professions and Biomedical Sciences in the field of **molecular epidemiology** and/or **epigenetics** as part of the University of Montana's NIH-funded Center of Biomedical Research Excellence (*COBRE*) in **Environmental Health Sciences** (**http://www.umt.edu/cehs**). The position is being offered at the Associate Professor/Professor level within the Department of Biomedical & Pharmaceutical Sciences of the Skaggs School of Pharmacy. We seek a candidate who will complement and expand existing research in the Center for Environmental Health Sciences (CEHS) and the Department, as well as interface with the College's program in Public Health. In addition, the candidate would assume the role of CEHS deputy director. Requirements include: a doctoral degree (M.D. and/or Ph.D.), a history of a successful research program, as evidenced by a strong publication record and previous/current funding, and a commitment to contribute to graduate and undergraduate educational programs. A competitive startup package will be provided.

The University of Montana is located in Missoula, a cosmopolitan Rocky Mountain community of about 80,000. The city has been singled out in national publications for its high quality of life. Abundant recreational opportunities in surrounding state and national forests and nearby Glacier National Park complement a thriving intellectual atmosphere.

Send letter of application, CV, statement of research goals, and three letters of reference to: Andrij Holian, Chair Molecular Epidemiology Search Committee, Department of Biomedical and Pharmaceutical Sciences, The University of Montana, Missoula, MT 59812; Telephone: 406-243-4018; FAX: 406-243-2807; email: **andrij.holian@umontana.edu**. Applications will be reviewed starting December 28, 2009 and will continue until the position is filled.

AA/EOE/ADA/Veterans Preference Employer

AIDS 2010

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JULY | 18-23 | 2010 | VIENNA AUSTRIA

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  Close 10 February 2010
- **SATELLITE APPLICATIONS**
  Close 31 March 2010
- **EXHIBITION SPACE APPLICATIONS**
  Close 31 May 2010

www.aids2010.org

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

JULIUS-MAXIMILIANS-UNIVERSITÄT WÜRZBURG, GERMANY

Research Center for Infectious Diseases

ZINF IMIB

YOUNG INVESTIGATOR POSITIONS

The Research Centre for Infectious Diseases (ZINF) of the University of Würzburg seeks two exceptional scientists for its young investigator program. We are interested in young scientists who have earned international recognition in the field of infectious diseases, microbiology, or host-pathogen interactions. Candidates using emerging or proven technologies to study new aspects of microbial pathogenesis are preferred, but all outstanding scientists are encouraged to apply.

Successful candidates will be appointed as group leaders for a period of 5+2 years. The salary (E14/15) will be commensurate with training and experience. The positions include laboratory operating expenses and salaries for additional personnel (post doc, graduate student, and technician). Laboratory space will be provided at a recently finished 9,000 m2 state-of-the-art research building with bio-containment, molecular imaging, high-throughput genomics, and animal facilities. The building is specifically designed to foster collaborative research, and houses six additional young investigator groups as well as laboratories run by faculty members. See www.infektionsforschung.uni-wuerzburg.de for more information. Informal inquiries about the posts can be made to Profs. Matthias Frosch (mfrosch@hygiene.uni-wuerzburg.de) or Jörg Vogel (vogel@mpiib-berlin.mpg.de).

Interested individuals should send, by **February 15, 2010**, a one-page description of research interests and future directions; curriculum vitae including list of publications; the names of three references. We may request short-listed candidates to submit a more detailed research proposal. The University of Würzburg is an equal opportunity employer. Women and individuals with disabilities are strongly encouraged to apply.

Applications should be sent **via email** to monika.meece@uni-wuerzburg.de, and addressed to the Spokesperson of the Research Center of Infectious Diseases, Prof. Dr. Matthias Frosch.

RHEINISCHE FRIEDRICH-WILHELMS-UNIVERSITÄT BONN

The Department of Chemistry at the Faculty of Mathematics and Natural Sciences of the University of Bonn invites applications for the position of a

Full Professor (W3) for Physical Chemistry (succession Prof. Wandelt)

at the Institute of Physical and Theoretical Chemistry. The appointment would begin October 1st, 2010. The successful candidate should have an excellent record of internationally recognized research in the field of physical chemistry and is expected to teach the entire physical chemistry curriculum. The existing research initiatives, e.g. the Collaborative Research Center 813 „Chemistry at Spin Centers" should be supported by current methods of physical chemistry, e.g. magnetic spectroscopy.

The conditions of employment are according to § 36 HG (NRW). University of Bonn is an Equal Opportunity Employer in compliance with German law. Applications of women and disabled applicants are particularly welcome.

Applications with the usual information (CV, documents of academic degrees, record of publications with up to five reprints, scientific profile, record of funding and given courses) should be sent before February 15th 2010 to:

Chairman of the Department of Chemistry
Prof. Dr. Alexander C. Filippou
Rheinische Friedrich-Wilhelms-Universität Bonn
Gerhard-Domagk-Str. 1
53121 Bonn
Germany

University of Minnesota

Department of Biochemistry, Molecular Biology and Biophysics

Tenure-Track Assistant Professor Systems and Computational Biology

The Department of Biochemistry, Molecular Biology and Biophysics invites applications for a full-time, tenure-track Assistant Professor position to begin on or around July 1, 2010. We seek candidates whose expertise complement existing Departmental strengths and who use both computational and experimental approaches to study problems in metabolic regulation related to diabetes, obesity, atherosclerosis, cardiovascular disease and/or cancer. For more details about the Department please consult: **http://cbs.umn.edu/BMBB/**.

The successful candidate will be expected to develop a strong, externally funded research program and contribute to the interdisciplinary undergraduate, graduate and professional teaching programs of the University in the area of systems and computational biology. Establishing collaborative partnerships across disciplines will be strongly encouraged. All candidates must have a Ph.D. and/or MD degree, applicable postdoctoral experience and a strong publication record.

The successful candidate will receive a substantial start-up package to establish their laboratory and a salary commensurate with education and experience. We will begin reviewing applications immediately and continue until the position is filled. Please apply online at employment.umn.edu, click on "Search Postings" and enter **164315** into the requisition number field. Please attach curriculum vitae and a brief statement of research plans (not to exceed 5 pages). Three letters of recommendation that consider both research and teaching potential should be sent to the **Faculty Search Committee, c/o Ms. Ann Johnson, Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, 6-155 Jackson Hall, 321 Church Street S.E., Minneapolis, MN 55455** or as an attachment to **swans143@umn.edu**.

The University of Minnesota is an Equal Opportunity Educator and Employer.

THREE TENURE-TRACK FACULTY POSITIONS AT UNIVERSITY OF TSUKUBA

Assistant Professor in Biostatistics/Public Health
Assistant Professor in Medical Sciences (any field)
Assistant Professor in Medical Pharmacology

The Medical Branch at Graduate School of Comprehensive Human Sciences has started four programs instructed in English under the **Global 30 Project** at University of Tsukuba **(http://www.global.tsukuba.ac.jp/en/index_e.htm)** and invites applications for three tenure-track positions at the level of **ASSISTANT PROFESSOR**, which are available from April 1, 2010.

Applicants should have a PhD and/or MD or equivalent recognized qualification in biomedical sciences and be able to demonstrate their potential as independent scientists. The successful applicants will be expected to establish and maintain extramurally funded research programs and to participate in teaching and training of medical and graduate students in English.

Applications including brief descriptions of education/research plans and philosophy (not to exceed two pages), one-page summary of teaching/practice experience, curriculum vitae, a list of publications (with copies of 5 most important ones) and three letters of recommendation should be filled in the forms downloaded from the website of Medical Branch at **http://www.md.tsukuba.ac.jp/G30/** and received by **January 15, 2010.**

Send applications to:
Head, Department of General Affairs, Medical Branch at Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tennodai 1-1-1, Tsukuba, Ibaraki 305-8575, Japan.
Tel: (81)-29-853-3023 or 3014 Fax: (81)-29-853-6387
E-mail applications in PDF files may be made to : iga9@un.tsukuba.ac.jp

For more information, visit our websites: **http://www.md.tsukuba.ac.jp/G30/, http://www.md.tsukuba.ac.jp/FrontierSite/global-30-english-programs**

Bioenergy Tenure-Track Faculty Positions

The University of Wisconsin-Madison is committed to improving our energy future through renewable energy research and discovery. To facilitate that commitment, UW-Madison's College of Agricultural and Life Sciences (CALS) formed the Wisconsin Bioenergy Initiative (WBI) to grow bioenergy expertise among UW-Madison, UW-System and Wisconsin stakeholders. The WBI is a university-based coalition that helps the talent within Wisconsin create, commercialize and promote bioenergy solutions. Its goal is to harness the talent, creativity and natural resources in Wisconsin to build a renewable energy landscape in our home state and beyond.

In order to advance these goals, UW-Madison is seeking individuals to grow bioenergy expertise in established departments with focus areas including, but not limited to: • Cell wall chemistry and deconstruction methods to enable methods of providing accessibility to the separate biopolymer fractions. • Biomass feedstock production to identify strategies to lower needs for fertilizer, high energy or high environmental cost agricultural chemicals. • Plant synthetic biology to understand and alter plant polymer/cell wall chemistry, biochemistry, cell biology and circuitry that controls the synthesis and deposition of these polymers. • Systems or synthetic biology to understand, computationally model, identify or improve microbial processes for conversion of plant biomass or other renewable resources into fuels. • Catalytic conversion methods to create fuels utiliizing routes of gasification, pyrolysis, liquification, upgrading and reforming. • Advanced batteries or other energy storage technologies, including the use of fundamental electrochemistry, new materials and integration of nanotechnology to enhance storage capacity, increase energy density and improve opportunities for implementation at large scales. • Biomass processing, aggregation and transport to connect the production of energy dense, highly consistent, readily convertible feedstocks with delivery to biorefineries and power plants. • Engineering expertise in current bioenergy processing methods, including dry and wet anaerobic digesters, gasification, pyrolysis and fluidized bed reactors for biopower. • Behavior change, public attitudes and social marketing, particularly in the energy sector. • Applied ethics and public policy to support the understanding of the social impacts of new energy technologies. • Ecological modeling which may include time series analysis, spatial statistics, hierarchical models and Bayesian statistics that can be applied to natural resource management, including assessment of bioenergy potential and impacts. • Community and regional development, with an emphasis on the economic and physical infrastructure needed for bioenergy development, and the analysis of social, cultural and land use impacts of bioenergy production, distribution and use.

The UW-Madison campus is located in the heart of the city of Madison, Wisconsin that offers an unsurpassed vibrant living and learning community. **(www.uc.wisc.edu/slideshow)** Applications, nominations, and inquiries are all invited. Review of applications began on **December 1, 2009**, and continue through **January 31, 2010**, or until successful candidates are identified. Please visit **www.wbi.wisc.edu/careers** for full position descriptions and submission instructions.

UW-Madison is an Equal Opportunity/Affirmative Action employer. Unless confidentiality is requested in writing, information regarding applicants must be released upon request. Finalists cannot be guaranteed confidentiality.

THE UNIVERSITY OF CHICAGO

The **University of Chicago's Institute for Biophysical Dynamics**, an interdisciplinary research institute at the interface of the physical and biological sciences, invites applications for the Institute's **Yen Fellowship**. This fellowship is for recent Ph.D. graduates and seeks to support outstanding individuals to undertake interdisciplinary research in the area of subcellular transport of macromolecules, using a combination of biophysical, genetic, computational, biochemical and cell biological tools. Yen Fellows are given considerable latitude in defining their research direction and will conduct their research in the laboratories of Institute faculty. A description of the Institute faculty and their research interests can be found at **http://ibd.uchicago.edu/directory.shtml_**.

We encourage applicants to contact Institute faculty directly about potential projects. Applicants should send their curriculum vitae, three reference letters and a short research proposal to **jfeder@uchicago.edu**. Review of applications will start on **15 January 2010**.

The University of Chicago is an Affirmative Action/Equal Opportunity Employer.

Head of Research,
Director of Charles Delaunay Institute

The Université de technologie de Troyes, **a high-end engineering school** based in the Champagne region, is launching an international search for the **Head of its research activities.**

Your mission: To lead and to coordinate the implementation of UTT's research strategy which you will contribute to define. As holder of a strategic position, you will also head the Charles Delaunay Institute, the organisational framework structure for UTT's eight research teams (140 staff members).

You are: either a University professor or a certified scientific in public or private institutions, with proven experience in running research activities. You have high-level knowledge in at least one of the scientific areas developed at the UTT, and thorough understanding of research environment and higher education in France and Europe. You know how to lead and inspire meetings and teams, assess programs and create favourable conditions for scientific project generation.

Kindly send your application to the attention of Mme Eva Zanczak, Direction des Ressources Humaines, UTT, 12 rue Marie Curie, 10010 Troyes Cedex, France, or by e-mail to eva.zanczak@utt.fr

utt
université de technologie Troyes

TENURE-TRACK FACULTY POSITIONS

THE HENRY SAMUELI SCHOOL OF ENGINEERING AT THE UNIVERSITY OF CALIFORNIA, IRVINE invites qualified applicants for two faculty positions beginning July 1, 2010. The positions are at the rank of Assistant Professor (tenure track) and will be formally associated with *The Edwards Lifesciences Center for Advanced Cardiovascular Technology*. Applicants must hold a Ph.D. in engineering or related fields. Individuals with interdisciplinary backgrounds and interest in joint appointments between Biomedical Engineering and any of the other engineering departments at UCI are also encouraged to apply. Successful candidates will be expected to maintain a broad-based extramurally funded research program. Research areas of interest include broadly the application of engineering technologies to address structural defects or disease in the cardiovascular system including, but not limited to, regenerative medicine (tissue engineering), photonic imaging and treatment, multiscale modeling, wireless communication systems, and biomedical micro- and nanoscale systems. In addition, the successful candidate will be expected to advise students and teach undergraduate and graduate courses relevant to biomedical engineering, as well as develop collaborative programs with other faculty members and programs at UCI. The University of California, Irvine is situated in Orange County's rapidly growing high technology sector that includes more than 300 biomedical companies. **APPLY NOW** – submit your application to our online recruitment program. For full consideration, candidates should upload applications electronically, please refer to the following website for instructions: **http://www.eng.uci.edu/employment/faculty/applicationinstructions**. Applications should include a curriculum vitae, a brief (no more than 2 pages) description of current and future research and teaching interests, and names of at least three references. Questions regarding these positions may be addressed to **Ms. Ruth M. Gratzer, rmgratze@uci.edu**. For more information about *The Edwards Lifesciences Center for Advanced Cardiovascular Technology* or the Department of Biomedical Engineering please visit our websites at **http://cardiovascular.eng.uci.edu** or **http://www.bme.uci.edu**. Applications will be accepted until the positions are filled, although maximum consideration will be given to applications received by **February 1, 2010**.

UCI is an Equal Opportunity Employer committed to excellence through diversity and strongly encourages applications from all qualified applicants, including women and minorities. UCI is responsive to the needs of dual career couples, is dedicated to work-life balance through an array of family-friendly policies, and is the recipient of an NSF ADVANCE Award for gender equity.

ESF

ASSISTANT/ASSOCIATE PROFESSOR

in Molecular and Cellular Biology

The Department of Environmental and Forest Biology at The State University of New York College of Environmental Science and Forestry (SUNY-ESF) in Syracuse, NY, invites applications for an academic-year, tenure-track position as an Assistant or Associate Professor in Molecular and Cellular Biology as applied to the environment or renewable resources. SUNY-ESF is seeking exemplary teacher-scholars who are committed to excelling in both teaching and research. Applicants must have a Ph.D. and one or more years of postdoctoral research experience and a high commitment to teaching at the undergraduate (and graduate) level. For a full position description, application requirements, and to apply online, see **www.esf.edu/hr/search/**

To ensure optimal consideration, all application materials must be received by **January 24, 2010**.

For more information contact William Powell at **wapowell@esf.edu**

SUNY-ESF is an Equal Opportunity/ Affirmative Action employer.

UNIVERSITY OF OSLO
FACULTY OF MEDICINE

Associate Professor/Professor position

available at the Department of Physiology, Institute of Basic Medical Sciences, University of Oslo, Norway. Tenured position with teaching duties (Faculty of Medicine). Applicants must establish an internationally competitive research program. The department has strong traditions and prominent international profile in neuroscience, circulatory physiology and cell biology. Current staff: 10 tenured faculty, 9 laboratory technicians and more than 30 PhD students and postdoctoral fellows.

More information at: **www.med.uio.no/imb/english** or Department Chair Joel C. Glover (**joel.glover@medisin.uio.no**).

Initial application (web-based) requires only CV and short statement of interest. Deadline January 6, 2010.

Apply at: **www.med.uio.no/felles/personal/ledigstilling/**

Nature Publishing Group, the publisher of *Nature*, is pleased to announce the launch of *Nature Climate Change*. This international monthly journal will launch in 2010 providing in-depth coverage on news and scientific- and impacts-based research relating to the Earth's changing climate.

Nature Climate Change will publish research crossing both natural and social sciences and will strive to forge and synthesize interdisciplinary research. The journal's mission will be to unify the body of research related to the understanding, and impacts, of Climate Change as well as putting the latest research into a wider social and political context.

We require a dynamic Chief Editor and two Associate Editors, based in our London offices, who are able to develop, launch and establish *Nature Climate Change* as the essential publication covering research into the Earth's changing climate. The ideal candidates will play a leading role in the accessibility of research, published in the journal, and its visibility in related research communities as well as the mainstream media and public.

Chief Editor Ref: NPG/104/09

Applicants must have a significant track record in climate-related research and, ideally, experience working in both the natural and social sciences. Candidates must be able to demonstrate a good understanding of the challenges faced by researchers, policy makers and other interested parties in understanding the complex mechanisms and impacts associated with our changing climate.

Associate Editors Ref: NPG/110/09

You will have a Ph.D. in a related discipline with demonstrable research achievements. Though postdoctoral experience is preferred (not required) emphasis will be placed on broadly trained applicants with knowledge of the broader research community. Key elements of the position include the selection of manuscripts for publication, and commissioning, editing and writing other content for the journal. We are ideally looking to recruit: one Associate Editor with a scientific understanding of the factors relating to the Earth's changing climate; and one Associate Editor with a social-economic understanding of the impacts and mitigation of climatic change.

These are demanding and extremely stimulating roles, which call for a keen interest in the practice and communication of science. The successful candidates will therefore be dynamic, motivated and outgoing, and must possess excellent managerial, presentation and interpersonal skills.

Applicants for the Chief Editor position should send a CV, a statement (1500 words maximum) that encapsulates their vision for the journal's content, competitive position and longer term development, and a brief cover letter detailing their salary expectations and explaining their interest in the post.

Applicants for the Associate Editor positions should send a CV (including their class of degree and a brief account of their research and other relevant experience), a News & View style piece (500 words or less) on a recent paper from related literature, and a brief cover letter detailing their salary expectations as well as explaining their interest in the post.

Applications should be sent to Diem Pham, HR Assistant at londonrecruitment@macmillan.co.uk Applicants should clearly mark on their submissions the reference number. Incomplete applications will not be considered.

Closing date: 4th January 2010

nature publishing group npg

THE UNIVERSITY of York

DEPARTMENT OF BIOLOGY

Lectureship in Eukaryotic Genetics Ref: UoY00590

Lectureship in Molecular Biophysics Ref: UoY00591

As part of a major expansion in biological and biomedical research activity at York, we are seeking outstanding and dynamic scientists with proven track records of high quality research to appoint as Lecturers in Eukaryotic Genetics and Molecular Biophysics.

Lectureship UoY00590 will be in an area of eukaryotic genetics that complements other research interests at York, with preference being given to individuals working with mammalian systems and/or genetic models of disease.

Lectureship UoY00591 would be particularly suitable for applicants investigating protein-DNA or protein-protein interactions using ensemble and/or single molecule biophysical methods.

Both appointees will be expected to develop independent research programmes of international standing aimed at understanding major biological or biomedical questions and to engage in teaching in related areas.

For informal enquiries, contact Professor Deborah Smith (dfs501@york.ac.uk; 01904 328843; UoY00590), Professor Colin Kleanthous (ck11@york.ac.uk; 01904 328820; UoY00591) or the Head of Department (Professor Dale Sanders, biohod@york.ac.uk; 01904 328555).

Salary will be within the range: £35,469 to £43,622 per annum.

For further information and to apply on-line, please visit our website: http://www.york.ac.uk/jobs/ Alternatively contact HR Services on 01904 434835 quoting the appropriate reference number.

Closing date: Thursday 21 January 2010

The University of York is committed to diversity and has policies and developmental programmes in place to promote equality of opportunity.

www.york.ac.uk

NEUROSCIENCE AND CELL BIOLOGY

A tenure-track/tenured position is available in The Department of Neuroscience and Cell Biology at the (UMDNJ) University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School. Investigators with interests in molecular neurobiology, cell biology and developmental neurobiology are encouraged to apply. In addition to being a member of the Department, the new hire will be provided opportunities within the neuroscience community at large with potential joint appointment in an appropriate department and/or center. The position will be available beginning July, 2010.

Please submit curriculum vita, summary of scientific interests and goals, and three letters of reference to: **Cheryl F. Dreyfus, Ph.D., Professor and Acting Chair. Address this material to Ms. Mary Beth Sparta, Department of Neuroscience and Cell Biology, UMDNJ-Robert Wood Johnson Medical School, 675 Hoes Lane West, Piscataway, NJ 08854-8021**. UMDNJ is an Affirmative Action/Equal Opportunity Employer, m/f/d/v, and a member of the University Health System of New Jersey.

UMDNJ ROBERT WOOD JOHNSON MEDICAL SCHOOL
University of Medicine & Dentistry of New Jersey

NUS National University of Singapore

APPOINTMENT OF OPERATIONS DIRECTOR LABORATORY ANIMAL FACILITIES NATIONAL UNIVERSITY OF SINGAPORE

The Comparative Medicine Centre (CMC) at the National University of Singapore **(http://www.nus.edu.sg)** provides professional and technical service for laboratory animal care, veterinary medical services, and animal research project support for staff and students of NUS. We now seek to appoint an operations director. This position holds full responsibility for the day to day management of all resources necessary for efficient conduct of animal experimentation and compliance with regulatory requirements across multiple sites in NUS. A detailed description of the job can be found at

http://www.nus.edu.sg/careers/potentialhires/currentvacancies/jobdesc/Professional/CMC.html

Applicants should have completed a relevant degree, and have a minimum of 5 years experience in a similar position. Extensive working and practical knowledge of animal husbandry is essential together with experience in managing and supervising staff.

The remuneration package will be commensurate with experience and qualifications appropriate to this senior position.

Applications (with a full CV and names of at least three referees) can be sent to:

Professor Peter Little
Office of the Deputy President (Research and Technology), NUS
University Hall, Lee Kong Chian Wing, UHL #05-02P
21 Lower Kent Ridge Road, Singapore 119077
Email: **dprpfrl@nus.edu.sg**

Closing date for applications: **30 Jan 2010**

UF UNIVERSITY of FLORIDA
The Foundation for The Gator Nation

FACULTY POSITIONS IN BIOMEDICAL ENGINEERING

The J. Crayton Pruitt Family Department of Biomedical Engineering at the University of Florida has multiple faculty openings as part of its plan to add 8 new faculty in the next several years as it adds an undergraduate program to its current MS and PhD programs. Candidates are expected to possess academic credentials sufficient to meet the requirements for full, associate or assistant professor appointments in Biomedical Engineering.

The BME Department has a mandate to be the research and educational interface between the highly ranked College of Engineering and the Health Sciences at Florida, including our excellent College of Medicine, the adjacent Veterans Administration facility, and the growing biomedical industry near Gainesville and in the state. Successful candidates will show promise to collaborate with our partners to form world-class research programs. Particularly promising areas include: imaging, computational bioinformatics, assistive technology, and drug delivery biologics, to target health care opportunities in the fields of aging, cancer, diabetes, and brain disease. The BME Department moved into its new building co-located with the College of Medicine, providing superb opportunities for interdisciplinary research, including the Shands Health Sciences Center, the McKnight Brain Institute, the NSF National High Magnetic Field Laboratory, the Cancer/Genetics Institute, the Nanoscience Institute for Medical & Engineering Technology, and institutional collaboration with the Moffit Cancer Center in Tampa. Translational biomedical engineering research will be facilitated by our recent NIH Clinical and Translational Science Award.

Independent of this announcement, the College of Engineering is planning to hire twenty new faculty in critical areas including computation, sustainable infrastructure, information technology, nano/microtechnology, energy, and health care/biotechnology.

Interested candidates should refer to our website: **http://www.bme.ufl.edu**. To ensure full consideration, application should be made by **March 1, 2010**, although the Search Committee will begin reviewing applications January 1, 2010.

The University of Florida is an Affirmative Action / Equal Opportunity Employer and women and minorities are encouraged to apply.

Confirmed featured speakers include:

Rita Colwell
Former Director, National Science Foundation; University of Maryland/Johns Hopkins University

Jay Keasling
DOE Joint BioEnergy Institute

MARCH 24-26 2010

Genomics of Energy & Environment

The 2010 Department of Energy Joint Genome Institute (DOE JGI) Genomics of Energy & Environment meeting will be held March 24-26 in Walnut Creek, California and specifically emphasize the genomics of renewable energy strategies, biomass conversion to biofuels, environmental gene discovery, and engineering of fuel-producing organisms.

The meeting will feature presentations by leading scientists advancing these topics: **Cristina Cuomo,** Broad Institute; **Evan Delucia,** University of Illinois at Urbana-Champaign; **Richard Flavell,** Ceres; **Dennis Hedgecock,** University of Southern California; **Madhu Khanna,** University of Illinois at Urbana-Champaign; **Steve Knapp,** University of Georgia; **Tom Mitchell-Olds,** Duke University; **Steve Moose,** University of Illinois at Urbana-Champaign; **Joseph Noel,** Salk Institute for Biological Studies; **Forest Rohwer,** San Diego State University; **Steven Savage,** Cirrus Partners; **Gary Stacey,** University of Missouri; **Jim Tiedje,** Michigan State University; **Detlef Weigel,** Max Planck Institute for Developmental Biology. The meeting will also include informatics workshops and tutorials for the analysis of prokaryotic and eukaryotic genomes, and the evaluation of new sequencing platforms and their applications.

Poster submissions are encouraged. Preregistration is required as interest is expected to exceed meeting capacity again this year. Registration and a preliminary agenda can be found at: www.jgi.doe.gov/usermeeting/

U.S. DEPARTMENT OF ENERGY
Office of Science

GRANTS

HUMAN FRONTIER SCIENCE PROGRAM (HFSP)

12 quai Saint-Jean, 67080 STRASBOURG Cedex, FRANCE

CALL FOR LETTERS OF INTENT FOR INNOVATIVE FRONTIER RESEARCH GRANTS: AWARD YEAR 2011

The Human Frontier Science Program supports **international** preferably **intercontinental** collaborations in basic life science research with emphasis placed on **innovative** and **interdisciplinary** approaches to fundamental investigations. Applications are invited for grants to support frontier approaches to understanding **complex mechanisms of living organisms**. Applicants are expected to develop **novel** lines of research distinct from their ongoing research. Preliminary results are not required.

There are two types of Grant: Young Investigators' Grants are for teams of scientists who are **all** within 5 years of establishing an independent laboratory and within 10 years of obtaining their PhDs. **Program Grants** are for independent scientists at all stages of their careers, although the participation of younger scientists is especially encouraged.

Grants provide 3 years support for 2 – 4 member teams, with not more than one member from any one country, unless critical for the **innovative** nature of the project, which is an important selection criterion. Applicants may establish a local or national interdisciplinary collaboration as a component of an international team but will be considered as 1.5 team members for budgetary purposes. Awards are dependent upon team size and successful teams will receive up to $450,000 per year. The principal applicant must be located in one of the member countries (Australia, Canada, the European Union, France, Germany, India, Italy, Japan, New Zealand, Norway, the Republic of Korea, Switzerland, the United Kingdom and the United States) but co-investigators may be located in any country.

Guidelines and further instructions are available on the HFSP web site (www.hfsp.org). International teams of scientists must first submit a letter of intent online via the web site. Specific enquiries: grant@hfsp.org

Deadlines : Compulsory pre-registration, via the web site: March 22nd 2010
Submission of Letters of Intent: March 31st 2010

Assistant Professor of Integrative Animal Physiology

Assistant Professor, 9-month appointment basis; Department of Animal Science College of Agriculture and Life Sciences, Cornell University.

The Department of Animal Science within the College of Agricultural and Life Sciences (CALS) invites applications for a tenure-track position as Assistant Professor of Integrative Animal Physiology. This is a continuing 9-month research (50%) and teaching (50%) position. The successful applicant will develop and lead an externally-funded research program devoted to the discovery of physiological mechanisms underlying the productivity, well-being and health of domestic animals. Physiological processes of interest include, but are not limited to, developmental programming, reproduction, lactation, growth, digestion and metabolism, and immune function. The research program should capitalize on opportunities to utilize state-of-the art core facilities in genomics, proteomics and transgenic animals. The use of domestic animals as biomedical models is desirable. Motivation to develop strong collaborations within the Department and across the University is essential. Teaching responsibility will include a primary role in delivering an introductory undergraduate course on domestic animal biology. Contribution to an advanced or graduate course in the appointee's disciplinary expertise, as well as advising and mentoring of undergraduate and graduate students is expected. ***Rank:*** Assistant professor, appointment on an academic year (9-mo) basis, tenure track. ***Closing Date:*** February 1, 2010 or until a successful candidate is identified. ***Date Available:*** July 1, 2010. ***Location:*** Department of Animal Science, College of Agriculture & Life Sciences, Cornell University, Ithaca, NY. ***Support:*** Laboratory space and an excellent start-up package will be offered. A competitive salary, commensurate with training and experience, and an attractive fringe benefits package, are provided.

Qualifications: A Ph.D. with training and demonstrated competence in integrated animal physiology. Postdoctoral experience, and an interest in domestic or companion animals are preferred. Applicants must be committed to both research and teaching excellence. ***Application:*** Send a complete resume, complete transcripts, a statement of research and teaching goals, and the names of at least three individuals who will provide letters of reference to: **W.R. Butler, Chairman Department of Animal Science, 149 Morrison Hall, Cornell University, Ithaca, NY 14853-4801, Phone: 607-255-2862 Fax: 607-255-9829, Email: wrb2@cornell.edu**

Cornell University, located in Ithaca, New York, is an inclusive, dynamic, and innovative Ivy League university and New York's land-grant institution. Its staff, faculty, and students impart an uncommon sense of larger purpose and contribute creative ideas and best practices to further the university's mission of teaching, research, and outreach.

Cornell University
Cornell University is an Affirmative Action/ Equal Opportunity Employer and Educator.

MASSACHUSETTS GENERAL HOSPITAL HARVARD STEM CELL INSTITUTE

The Center for Regenerative Medicine (CRM) at Massachusetts General Hospital invites applications for a tenure-track Assistant Professor position. Outstanding scientists in the field of vertebrate stem cell or regenerative biology will be considered. Candidates with a research program focused on adult stem cell biology, tissue regeneration, pluripotency, neuroscience, or organ biology and who have an interest in application to human disease are especially welcome. Successful candidate(s) will be members of the **Harvard Stem Cell Institute** and faculty of **Harvard University**. Candidates must hold a PhD and/or MD and have a history of innovative, interactive research.

Applicants should send an electronic copy of (1) letter of interest (2) research plan and (3) current curriculum vitae to **Miklosik.Mona@mgh.harvard.edu**. Three letters of recommendation should also be sent directly to: **Center for Regenerative Medicine Search Committee, Attention: Mona Miklosik, Massachusetts General Hospital, 185 Cambridge St., CPZN 4258, Boston, MA 02114**.

Women and minority candidates are urged to apply. MGH is an Equal Opportunity/ Affirmative Action Employer.

CLINICAL ASSISTANT PROFESSORS Department of Biology ARTS AND SCIENCE

The Department of Biology at New York University invites applications for two Clinical Assistant Professor appointments to start September 1, 2010, pending budgetary and administrative approval. Responsibilities include developing and teaching curriculum in Genetics, Genomics or Microbiology as well as teaching several Principles of Biology Laboratory sections. Previous research and teaching experience is preferred. The Department of Biology (**http://biology.as.nyu.edu**) offers an outstanding and collegial research environment. Opportunities exist for active collaborations with related divisions within the University.

Candidates should submit a single PDF file containing Cover Letter, CV, and Teaching Statement that outlines interest and experience to **biology.clinicalsearch@nyu.edu**. The following address can be used for the cover letter: **Dr. Gloria Coruzzi, Department of Biology, New York University, 1009 Silver Center, 100 Washington Square East, New York, NY 10003**. Three PDF letters of reference should also be submitted separately to **biology.clinicalsearch@nyu.edu**. *Closing date for all materials is* ***January 29, 2010***.

NEW YORK UNIVERSITY

NYU is an Equal Opportunity/Affirmative Action Employer.

National Engineering Laboratory for Anti-Tumor Protein Therapeutics
抗肿瘤蛋白质药物国家工程实验室

Postdoctoral Fellows in Cancer Biology

The National Engineering Laboratory for Anti-tumor Protein Therapeutics focuses on both basic and translational tumor research with the ultimate goal of developing molecularly targeted cancer therapeutics. We will provide compensation relative to US standards for highly qualified and motivated postdoctoral fellows with strong interests in tumor progression and metastasis.

Successful candidates will have received a Ph.D./M.D. in areas related to cancer biology. Applicants should have a strong background in cancer biology, immunology, molecular and/or cellular biology, as well as an excellent publication record in related fields. Applicants should have excellent communication skills in English, be highly motivated, and be able to work within a multidisciplinary team.

The successful candidates will be expected to undertake independent projects in cancer research, especially related to tumor metastasis, tumor immunology, and tumor angiogenesis/lymphangiogenesis. Experience with genetic animal models, biomarker discovery, drug design and tumor pathology is preferred. Compensation will be competitive to US standards, and will be determined based on the assessment of the candidate's application and subject to sufficient funding. Upon successful completion of the postdoctoral training, there are also potential opportunities for faculty positions.

Positions are available immediately and applications will be received on a rolling basis until all positions are filled. Applicants should send a cover letter indicating research interests, CV, and the names of three references to:

Yongzhang Luo, Professor, Director
National Engineering Laboratory for Anti-tumor Protein Therapeutics
School of Life Sciences, Tsinghua University
Beijing 100084
P. R. China
Tel: 86-10-6277-2897
Fax: 86-10-6279-4691
E-mail: **yluo@tsinghua.edu.cn**
Website: **www.antitumor.org; www.luolab.org**

SYRACUSE UNIVERSITY

The Beverly Patterson Bishop Professorship in Neuroscience (025753)

The College of Arts and Sciences at Syracuse University invites applications for the Beverly Patterson Bishop Professorship in Neuroscience. This is a tenured and endowed professorship at the rank of Associate Professor or Professor, depending upon the experience and qualifications of the successful applicant. We seek candidates with an interdisciplinary approach to neuroscience questions whose research and teaching exhibit innovation and excellence. We will consider applications from those engaged in outstanding neuroscience research in all areas across the spectrum from molecules to mind. Given the interdisciplinary nature of the position, the academic appointment of the successful candidate could be in one or more of the following departments of the College: Biology, Chemistry, Communication Sciences and Disorders, Physics and/or Psychology. In addition, joint appointments in academic departments at the State University of New York-Upstate Medical University are possible. Neuroscience is an emerging interdisciplinary initiative at Syracuse University and the successful candidate will be expected to foster the growth of this initiative. The successful candidate will have a strong history of scholarly activity and an ongoing, independent research program that complements this collaborative framework. Job requirements include a Ph.D. degree and teaching at the undergraduate and graduate levels.

The collaborative interactions between Syracuse University and neighboring campuses provide rich interdisciplinary opportunities that include theoretical/computational neuroscience, developmental biology, evolutionary biology, cognitive neuroscience, and behavioral, clinical, cellular or molecular neuroscience. A list of equipment and links to potential collaborators is available at: **http://thecollege.syr.edu/student/home.htm** (click on Bishop Professorship link).

Candidates must visit **www.sujobopps.com** to complete a Dean/Senior Executive/Faculty application form and attach a current curriculum vitae plus (1) a cover letter outlining the candidate's qualifications, (2) a brief statement of research interests and future goals, and (3) a summary of teaching experience and teaching interests. Personal inquiries may be directed to:

Bishop Neuroscience Faculty Search (c/o J.M. Russell)
Department of Biology
107 College Place
Syracuse University
Syracuse, NY 13244
E-mail: jrussell@syr.edu

Priority will be given to applications received prior to January 15, 2010.

Syracuse University is an Affirmative Action/Equal Opportunity Employer.

HARVARD UNIVERSITY

Assistant/Associate Professors
Department of Genetics and Complex Diseases

The Department of Genetics and Complex Diseases (GCD) at the Harvard School of Public Health (HSPH) invites applications for tenure-track positions at the level of assistant professor. Exceptional associate professor candidates will also be considered. Successful applicants will hold a PhD and/or MD degree and will have a record of outstanding productivity. Individuals are sought particularly in the following areas to complement the existing research and training goals of the department: signal transduction related to energy and nutrient sensing pathways, regulation of metabolic homeostasis, inflammatory and stress response pathways related to chronic metabolic diseases and aging, cancer metabolism, and epigenetic regulation of metabolism. Individuals using systems and/or computational approaches applied at a mechanistic level to problems of metabolic homeostasis, gene-environment interactions and/or adaptive responses are also encouraged to apply. The candidate should possess the ability to work collaboratively with other scientists and the scholarly qualities required to mentor doctoral students in the graduate program in the Division of Biological Sciences. Generous start-up packages and state-of-the-art research facilities are available.

Please send a letter of application, including a statement of current and future research interests, curriculum vitae, sample publications, and the names of four references to the following address. Applicants should ask their four references to write independently to this address:

Chair, GCD Search, c/o Audrey Harmon
Department of Genetics & Complex Diseases
655 Huntington Avenue, Building II, 113
Boston, MA 02115
gcddept@hsph.harvard.edu

The Harvard School of Public Health is committed to increasing the representation of women and minorities in its faculty, and encourages applications from such candidates.

Postdoctoral Positions

Miami Institute of Molecular Imaging and Computation (MIMIC) at the University of Miami seeks motivated scientists to join an innovative, cross-disciplinary and imaging-intensive project on *in situ* protein-protein interaction networks, or isPIN. This collaborative project aims to redefine proteomics as a context-rich molecular bioinformatics. The current goals of the isPIN project are to create transgenic Drosophila expressing imaging-ready neuronal proteins, reveal their localization and direct association within model neurons, and construct context-specific proteomic maps of wild type neurons in the intact nervous system. More information is available at **www.miami.edu/ispin**. Two postdoctoral research associate positions are available immediately and renewable for three years. Each position requires a PhD degree or equivalent and expertise in one or more of the following: molecular imaging, neuroscience, biochemistry, biophysics, bioinformatics, systems biology, high-performance computation, robotics, and high-content analysis. These positions offer opportunities to extensively interact with faculties of neuroscience, computer science and biology, gain knowledge on various technologies including Drosophila genetics, 3D FLIM and cross-correlational analysis, and develop own ideas for unique projects. The current phase of the project is funded in part by an ARRA grant from NIH. Submit resume to Dr. Akira Chiba, Department of Biology, University of Miami, Coral Gables, Florida 33146, USA (email: **akira.chiba@miami.edu**).

CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF MEDICINE

Tenure Track Faculty Positions in RNA Molecular Biology

The Center for RNA Molecular Biology, Case Western Reserve University School of Medicine (a freestanding unit in the basic sciences) invites applications for two tenure track Assistant Professor positions. Because these positions are supported in part by a P30 faculty recruitment grant from the NIH, we are seeking candidates in two specific areas:

1. **Bioinformatics** – Candidates in this area will be expected to have made significant contributions to RNA biology using state-of-the-art bioinformatics approaches and be able to develop a strong independent research program using such approaches. In addition, the successful applicant will participate in the hiring and supervision of an individual who will provide informatics support for faculty throughout the CWRU research community whose projects involve RNA analysis including high throughput sequencing.
2. **Genome wide approaches** – Candidates in this area will be expected to have made significant contributions to our understanding of RNA biology using genome wide approaches and be able to develop a strong independent research program using such approaches. We are particularly interested in candidates who plan to analyze large non-coding RNAs, small regulatory RNAs or investigate RNA-protein interactions at a genome wide level.

Applicants should provide via email a current CV, a statement (2-3 pages) of their research plans, and the names of four references to: **twn@cwru.edu**. Non-electronic submissions may be mailed to: **Center for RNA Molecular Biology, Attn: Dr. Timothy Nilsen, SOM-Wood-W127, 10900 Euclid Ave., Cleveland, OH 44106-4973**. Evaluation of candidates will begin immediately.

In employment, as in education, Case Western Reserve University is committed to Equal Opportunity and Diversity. Women and underrepresented minorities are encouraged to apply. CWRU is a past recipient of a National Science Foundation ADVANCE Institutional Transformation Award to increase the participation of women in Science and Engineering.

Additional information about the Center for RNA Molecular Biology can be found at: **http://www.case.edu/med/rnacenter/home.htm**.

KRISS 한국표준과학연구원
Korea Research Institute of Standards and Science

KRISS: The Cradle of Fundamental Science Research

Korea Research Institute of Standards and Science (KRISS) is a government-funded, public research institute that has actively worked on fundamental science and key technologies.

In KRISS, you will have the opportunities to join the expert group capable of conducting convergence research in various fields of science and to enjoy challenging and creative research projects.

KRISS is looking for competent researchers who want to work together for our goal of producing the first Nobel Science Prize laureate in Korea. Take up the challenge and open up your dreams and passion with KRISS!

Job Openings

■ Full-time positions

Research Centers	Areas of Openings	
Center for Electricity and Magnetism	Development of new measurement technology in electric and magnetic standards	Physics, Electric/ Electronic Engineering
Center for Bioanalysis	Development of measurement standards and techniques for proteins and clinical	Analytical Chemistry, Analytical Biochemistry
Center for Brain and Cognitive Science Research	Development of ultra low field magnetic resonance imaging and signal processing	Physics, Electric/ Electronics Medical Engineering

■ Postdoctoral fellowships

Positions are available in the following areas : Chemistry, Bioscience, Environment, Biotechnology, Chemical Engineering, Medical Science, Brain and Cognitive Sciences, Aesthetic Engineering; Physics, Electric/Electronics, Materials Science and Engineering, Mechanical Engineering, other science and technology disciplines.

Qualifications

Candidates of all nationalities are invited to apply. Those who apply for full-time positions or postdoctoral fellowships shall demonstrate their R&D abilities through publication of their works in scientific or engineering journals and/or registration of patents as the principal inventor with the patent office in the US, Europe or Japan.

All applicants must be able to demonstrate the ability to develop and to work effectively on multiple concurrent projects in a collaborative, multidisciplinary team environment. Being flexible and having a demonstrated ability to master new technical areas are also desirable.

Information

Successful candidates will be provided with privileges as follows

Full-time positions	Postdoctoral Fellowships
Accommodation & Migration fee	Salary ($40,000 - $41,000 a year) 1 or 2 year(s) of employment Accommodation & Migration fee

Other Information

Applications will be open until Dec. 30, 2009. Submitted documents will not be returned. Documents containing false data will be nullified. Should you need any detailed information or have inquiries, either visit **http://english.kriss.re.kr**, or contact us at **job@kriss.re.kr** or **+82-42-868-5511.**

march 8-9, 2010
Arizona Biltmore | Phoenix, Arizona

personalized medicine in the clinic:

policy, legal, and ethical implications

This national conference with top experts will examine the impact of personalized medicine on the delivery of healthcare in the future. Conference highlights:

patient rights
medical privacy and confidentiality
ethics
individualized medical care
economics
liability issues for physicians

For CLE and CME information and to register, visit www.law.asu.edu/personalizedmedicine2010.
To become a conference supporter, call 480.965.2465.

Conference co-sponsors:

CENTER FOR THE STUDY OF LAW, SCIENCE, & TECHNOLOGY

ASU Sandra Day O'Connor College of Law, Arizona State University

MAYO CLINIC

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MEN2 Thyroid Cancer Research Scholar, Mentored Research Scholar, and Postdoctoral Fellows:

A Request for Applications

Research Scholar Grant Eligibility Expanded to Include Independent Investigators at any Career Stage

Next Receipt Deadline: April 1, 2010

The American Cancer Society announces this revised **Request for Applications** for the **American Cancer Society MEN2 Thyroid Cancer Consortium**. ***Funds remain available*** for up to seven (7) **Research Scholar** and/or **Mentored Research Scholar** grants and up to five (5) **Postdoctoral Fellow** grants will be awarded. The Consortium will be led by a single renowned senior scientist who will be awarded the American Cancer Society MEN2 Thyroid Cancer Professorship and act as leader for the overall program (details at links below). Appropriate areas of investigation include, but are not limited to: understanding consequences of *RET* mutations, molecular events underlying the development of MEN2-related tumors, improved animal models of MEN2, new screening and monitoring tools, new imaging approaches, and new pharmacologic and other strategies to blunt the effects of mutations in *RET* and other genes associated with medullary thyroid cancer.

Individuals applying for a **Research Scholar Grant** must have an independent research or faculty position *and can be at any stage of their career*. These grants will be awarded for up to $200,000 a year, direct costs, for 5 years. **Mentored Research Scholar Grants** will be awarded to junior faculty members with a doctoral degree in a clinical or cancer control research discipline (e.g., M.D., and/or Ph.D.) that are within the first four years of a full time faculty appointment or equivalent, and have no more than 4 years of postdoctoral research experience immediately prior to their faculty appointment. The successful applicant is expected to transition into a career as an independent investigator. Awards are for up to five years and for up to $135,000 per year direct costs.

Applicants for **Postdoctoral Fellowships** must have obtained their doctoral degree prior to activation of the fellowship. Awards are for three years with progressive stipends of $44,000, $46,000, and $48,000 per year, plus a $4,000 per year institutional allowance. Individuals who have held a PhD or MD and have been doing research for more than 4 years at the time of application are not eligible.

Deadline: Complete applications are due by **April 1, 2010**. Funding will begin January 1, 2011. For information regarding funding policies or to obtain an application, go to **https://proposalcentral.altum.com** or refer to the ACS website at **www.cancer.org/research**: select *Funding Opportunities* followed by *Index of Grants*, scroll down to *Special Initiatives* and select the appropriate RFA for MEN2 Thyroid Cancer. For inquiries, contact **Charles Saxe, PhD** at **(404) 929-6919 (charles.saxe@cancer.org)**.

Canada Research Chair (Tier I) in Emerging Pathogens Director of the Emerging Pathogens Research Centre

uOttawa
L'Université canadienne
Canada's university

Applications are invited for a Tier I Canada Research Chair (CRC) in Emerging Pathogens, who will hold a tenure-track position at the level of Full Professor. The incumbent will also become Director of the new Emerging Pathogens Research Centre (EPRC). The University of Ottawa, a Canadian leader in biomedical research, is undergoing a major expansion of its basic science research capacity, including the area of emerging pathogens and infectious disease. The EPRC focuses on infection models of viruses, bacteria, and prions; innate and adaptive immunity including vaccinology and therapeutic resistance; the support of research programs involving populations and epidemiology, bioinformatic, translational, genomic, evolutionary and systems approaches dealing primarily (but not exclusively) with the nervous, respiratory, hematologic, and enteric systems. The candidates are expected to be international leaders in infectious diseases and/or emerging pathogens research. They also need to display excellent leadership qualities and a vision that will foster the growth of the Research Centre. The Director will be expected to enhance the research activities of the Centre via multiple strategies, including the recruitment of more junior scientists. Applicants should have a Ph.D. and/or M.D. degree. The ability to teach in both French and English would be an asset.

Interested applicants are invited to submit an application consisting of the following: a curriculum vitae, a short statement of their research goals and objectives and the names of three persons able to supply letters of reference. The application package should be sent by post, courier, or e-mail to: **Dr. Earl Brown, Executive Director of the Emerging Pathogens Research Centre, Department of Biochemistry, Microbiology and Immunology, Faculty of Medicine, University of Ottawa, 451 Smyth Road, Ottawa, Ontario, K1H 8M5. Email: ebrown@uottawa.ca**. The review of applications will begin in January 2010 and the process will continue until the position has been filled.

All qualified candidates are encouraged to apply; the Canada Research Chairs Program imposes no restrictions on nominees with regard to nationality or country of residence. Procedures to allow non-Canadian chairholders to work in Canada have been established by Human Resources and Skills Development Canada and Citizenship and Immigration Canada. Equity is a University of Ottawa policy; women, Aboriginal peoples, members of visible minorities and persons with disabilities are encouraged to apply. At the time of tenure, professors are expected to have the ability to function in a bilingual setting.

Vanderbilt University Medical Center

Department: Center in Molecular Toxicology and the Vanderbilt Institute for Clinical and Translational Sciences

Position: Integrative Health Sciences Facility Core Research Program Coordinator. The Center in Molecular Toxicology and the Vanderbilt Institute for Clinical & Translational Research at Vanderbilt University School of Medicine seek candidates for a Research Assistant Professor or Research Associate Professor position in the non-tenure research track to lead a newly created and novel Integrative Health Sciences Facility Core, the goals of which are to promote and develop translational research in the environmental health sciences. Applicants must have a Ph.D., M.D., or equivalent degree, and have demonstrated excellent qualifications in research, preferably in environmental sciences. In addition, specific expertise in research project coordination (i.e., research design and project organization, collaboration, basic analytic skills, and program development, etc.), and manuscript and grant writing experience are essential. Excellent verbal and written communication skills, as well as the ability to work in a team are essential.

This is an ideal position for someone who may desire to transition from being a PI to a non-tenure track salaried position, with the opportunity to lead and facilitate new and novel research directions and opportunities for funding in the environmental sciences. Significant infrastructure resources exist to develop unique integrative and translational research programs with world-renowned scientists.

Please submit curriculum vitae, and a letter of interest to:
Tina V. Hartert, MD, MPH
Vanderbilt University School of Medicine
6107 Medical Center East
Nashville, TN 37232-8300
(615) 936-1010
tina.hartert@vanderbilt.edu

Vanderbilt University School of Medicine is an equal opportunity, affirmative action employer. Women and minority candidates are strongly encouraged to apply.

CONFERENCE

PRIZES

INSTITUT DE FRANCE

INSTITUT DE FRANCE
Académie des sciences

Call for applications for the Cino del Duca Prize for Science

The Simone and Cino del Duca Foundation of the Institut de France will award its 2010 Prize (364000 €) to a European team working in the field of

"Vectorisation of bioactive compounds for therapy of major pathologies"

Applications should be sent before February 11th, 2010 to :
fondation-del-duca@institut-de-france.fr

For additional information, please contact the Simone and Cino del Duca Foundation of the Institut de France

Tel : 00 33 (0)1 47 66 01 21
Fax : 00 33 (0)1 46 22 45 02

The application form can be downloaded on the following site

www.actualites.institut-de-france.fr

2010 Cold Spring Harbor Laboratory Meetings & Courses

Meetings

Neuronal Circuits
March 10 -13 abs due January 8

PTEN Pathways & Targets
March 16 - 20 abs due January 15

Systems Biology: Global Regulation of Gene Expression
March 23 - 27 abs due January 15

RNA & Oligonucleotide Therapeutics
April 7 - 10 abs due January 22

Gene Expression & Signaling in the Immune System
April 21 - 25 abs due January 29

Vertebrate Organogenesis
April 27 - May 1 abs due February 5

Molecular Chaperones & Stress Responses
May 4 - 8 abs due February 12

The Biology of Genomes
May 11 -15 abs due February 19

The Cell Cycle
May 18 - 22 abs due February 26

Retroviruses
May 24 - 29 abs due March 5

75th Symposium: Nuclear Organization & Function
June 2 - 7 abs due March 12

Glia in Health & Disease
July 22 - 26 abs due May 7

Mechanisms & Models of Cancer
August 17 - 21 abs due May 28

Molecular Genetics of Bacteria & Phages
August 24 - 28 abs due June 4

Nuclear Receptors & Disease
August 31 - September 4 abs due June 11

Personal Genomes
September 10 -12 abs due June 18

Translational Control
September 13 - 17 abs due June 16

Axon Guidance, Synaptic Plasticity and Regeneration
September 21 - 25 abs due July 2

Molecular Genetics of Aging
September 28 - October 2 abs due July 9

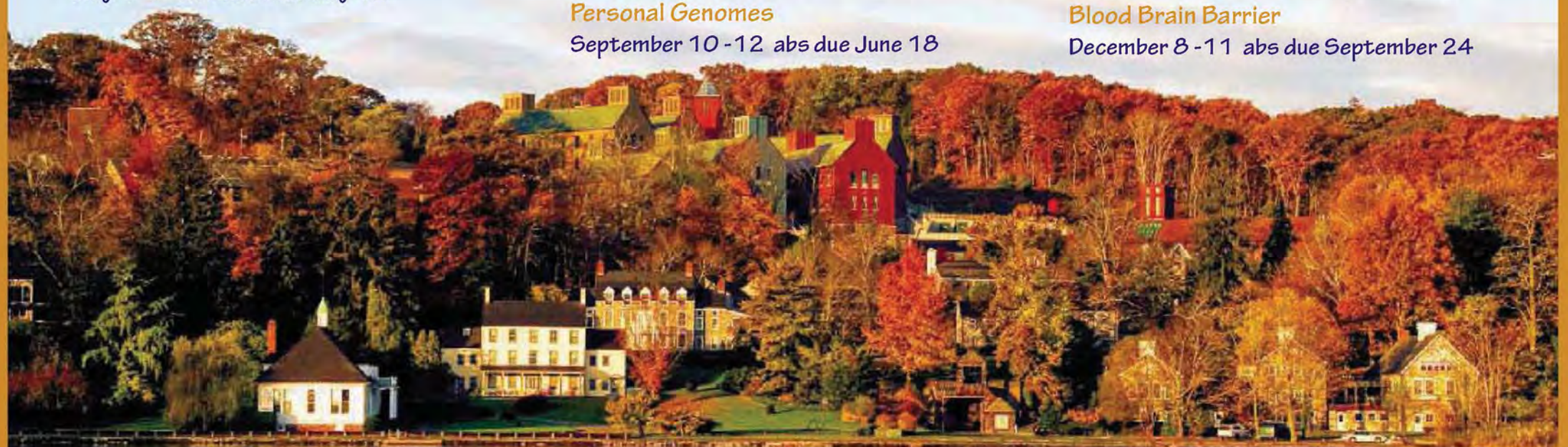
Germ Cells
October 5 - 9 abs due July 16

Mouse Development, Genetics & Genomics
October 26 - 30 abs due August 6

Pharmacogenomics & Personalized Therapy
November 17 - 21 abs due September 3

Neurodegenerative Diseases: Biology & Therapeutics
December 1 - 4 abs due September 17

Blood Brain Barrier
December 8 -11 abs due September 24



Courses

Protein Purification & Characterization
April 7 - 20

Cell & Developmental Biology of *Xenopus*
April 9 - 20

Workshop on Schizophrenia & Related Disorders
June 9 - 15

Advanced Bacterial Genetics
June 9 - 29

Ion Channel Physiology
June 9 - 29

Molecular Embryology of the Mouse
June 9 - 29

Integrated Statistical Analysis of Genome Scale Data
June 16 - 29

Computational Neuroscience: Vision
June 18 - July 1

Computational Cell Biology
July 2 - 22

Genetics of Complex Human Diseases
July 6 - 12

Molecular Techniques in Plant Science
July 2 - 22

Neurobiology of *Drosophila*
July 2 - 22

Advanced Techniques in Molecular Neuroscience
July 6 - 22

Workshop on Biology of Social Cognition
July 14 - 20

Brain Tumors
July 22 - 28

Proteomics
July 22 - August 4

Eukaryotic Gene Expression
July 27 - August 16

Imaging Structure & Function in the Nervous System
July 27 - August 16

Yeast Genetics & Genomics
July 27 - August 16

Stem Cells
July 30 - August 5

C. elegans
October 11 - 26

Programming for Biology
October 11 - 26

X-Ray Methods in Structural Biology
October 11 - 26

Advanced Sequencing Technologies & Applications
October 13 - 26

Immunocytochemistry, *In Situ* Hybridization, Super-Resolution & Live Cell Imaging
October 13 - 26

Phage Display of Proteins & Peptides
November 2 - 15

Computational & Comparative Genomics
November 3 - 9

The Genome Access Course
April 27 - 28, November 16 - 17

Cold Spring Harbor Laboratory Meetings & Courses Program, 1 Bungtown Road, Cold Spring Harbor, NY 11724
Phone: 516 367 8346 email: meetings@cshl.edu www.cshl.edu/meetings

POSITIONS OPEN

POSTDOCTORAL POSITION available in **Dr. Bruce Lahn's** lab at Howard Hughes Medical Institute, Dept of Human Genetics, University of Chicago. The position involves highly novel research projects that intersect stem cell biology, epigenetics, and functional genomics. Experience with cell and molecular biology desirable; experience with bioinformatics especially valued. Dr. Lahn's research is described at **website: http://www.genes.uchicago.edu/lahn.html.** Please send inquiries to **e-mail: blahn@bsd.uchicago.edu.**

The School of Natural Resources, University of Nebraska-Lincoln is seeking an **ASSISTANT PROFESSOR** (tenure-track, nine month appointment) to conduct basic and applied research in aquatic ecology and limnology with a focus on surface water in Nebraska. Areas of expertise may include algal community composition, water resource classification, abiotic-biotic interactions, and other topics that improve our understanding of the structure and function of surface water ecosystems. The individual will be required to teach undergraduate and graduate courses in aquatic ecology, limnology and water quality that contributes to the B.S. degree in Water Science. The individual will be expected to develop external funding in support of their research and teaching program, and supervise undergraduate and graduate students; publish research and teaching results in scholarly literature and refereed publications and present findings at various venues. Additional responsibilities include collaboration with other UNL faculty to enhance the teaching mission of SNR, advise/mentor undergraduate water science students and graduate students, and other duties as assigned. The individual will be expected to average 0.30 teaching FTE or greater. As part of a recent campus-wide initiative, which integrates activities in water science, engineering, policy, and law, the position advertised here complements recent Water Initiative hires in aquatic chemistry, river ecology, water law, water economics, water policy, climate modeling, physical limnology, environmental engineering and hydroinformatics, as well as several anticipated water-related faculty positions in the near future. We seek a highly motivated individual who is willing to take an active role in promoting research, education, and interdisciplinary interactions associated with this broader initiative.

To apply, go to **website: http://employment.unl.edu** requisition #090713 and complete the "Faculty Academic Administrative Information form." Applicants must attach a cover letter, curriculum vitae, statement of research and teaching interests, and names and complete contact information for at least three references. Review of applications will begin on February 1, 2010, but the position will remain open until filled or is closed.

The University of Nebraska has an active National Science Foundation ADVANCE gender equity program, and is committed to a pluralistic campus community through affirmative action, equal opportunity, work-life balance, and dual careers.

POSTDOCTORAL POSITION in MATHEMATICAL MODELING of INFECTIOUS DISEASES

Seeking highly motivated **Postdoctoral Fellow** to work with a multidisciplinary team of modelers, epidemiologists, laboratory researchers, and clinicians on an NIH-funded, multi-year project investigating the ongoing transmission of tuberculosis (TB) and drug resistant TB in Peru. This position is for two years, with the possibility of extension. Start date is March 1, 2009.

Successful candidates should have received a recent Ph.D. or M.D., be committed for a minimum of two years, have a strong record of training in mathematical modeling, and must be highly committed to establish an independent career in research in infectious disease modeling. Please send your CV, statement of research accomplishments and interests, and contact information for three references by e-mail to: **Megan Murray, M.D., Sc.D. Phone: 617-432-2781. E-mail: mmurray@hsph.harvard.edu.**

POSITIONS OPEN

UNIVERSITY OF MIAMI
MILLER SCHOOL of MEDICINE

THE MIAMI PROJECT TO CURE PARALYSIS
Department Of Neurological Surgery
University Of Miami Miller School Of Medicine
FACULTY POSITION:
Principal Investigator
Reparative Strategies In Spinal Cord Injury

The Miami Project to Cure Paralysis/Department of Neurological Surgery at the University of Miami, Miller School of Medicine is seeking outstanding applicants at the **ASSISTANT, ASSOCIATE** or **FULL PROFESSOR** levels. A significant record of academic accomplishment and the potential to attract independent research funding are important considerations for this position. The Miami Project offers excellent basic science, translational, and clinical research programs directed toward study of central nervous system damage and development of novel treatments to promote functional recovery.

The successful applicant (Ph.D. and/or M.D.) will be a member of this interdisciplinary Center of Excellence with access to numerous state-of-the-art core facilities. The candidate should have a strong interest in pursuing research related to reparative strategies for spinal cord injury. Investigators using cell based therapies and biomaterials in animal models are of particular interest but other approaches are also encouraged. Rank and salary will commensurate with experience and record of academic accomplishment.

This is an excellent opportunity to join a productive team of basic and clinical scientists investigating spinal cord injury in a state-of-the-art research center located in a beautiful city. Start-up packages, salaries and benefits are commensurate with experience. The positions are available July 1, 2010. Those interested should email their curriculum vitae, names and contact information for three references, and a brief summary of their research interests and goals to **e-mail: jcox@med.miami.edu.** Include "Faculty search" in the subject line.

The University of Miami Miller School of Medicine is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.

Applications are invited for a **POSTDOCTORAL POSITION** with zero to two years experience, in the **Department of Target Discovery and Cellular Microbiology** at the **US Army Medical Research Institute of Infectious Diseases (USAMRIID),** Frederick, Maryland.

Candidates should have a background in computational biology, biophysics, or systems biology, and be experienced in numerical analysis/programming (e.g. C++, MATLAB or others). Good written and communication skills, and a high level of motivation and commitment are required. The applicant will translate the imaging biological systems data (based on single cell phenotypic measurements) into novel computational models that allow the spatiotemporal and quantitative prediction of signaling events and the identification of key regulatory factors or new compound mechanisms. The interdisciplinary working environment spanning the fields of systems biology, immunology, imaging and infectious disease research will provide unique opportunities and exposure to cutting-edge technologies. The ultimate goal of this research program is to develop an understanding of the infectious disease processes and response to drugs at the cellular and molecular level.

Requirements include a Ph.D. in cell biology, immunology, statistics, computational biology or related bioinformatics disciplines, and a record of academic productivities. Preference will be given to candidates who have experience with advanced techniques for analyzing imaging data, and/or system biology data. A strong interest in integrated analysis of high throughput phenotype data would be highly desirable, as would strong programming experience using Matlab, R, SAS, and/or C/C++.

Please submit a letter of intent and updated CV to **e-mail: rekha.panchal@amedd.army.mil.**

POSITIONS OPEN

VIROLOGY SEARCH: ASSOCIATE OR FULL PROFESSOR
Department of Microbiology and Core Staff Scientist, Washington National Primate Research Center
University of Washington

The Department of Microbiology and the Washington National Primate Research Center at the University of Washington in Seattle are conducting a search for an **ASSOCIATE** or **FULL PROFESSOR** in the field of HIV/SIV virology. We are looking for an innovative investigator with a robust independent research program studying viral immunology, viral pathogenesis, virus-host interactions, or systems virology, and using non-human primate models of HIV infection. The position is a 12-month, full time, position in the School of Medicine, and is funded by the Primate Center Core Grant, now in its 48th year, and by the Department of Microbiology. The position provides an opportunity to join a dynamic, interactive community of virologists and immunologists investigating HIV/SIV virology, pathogenesis and vaccines. All University of Washington Faculty engage in undergraduate or graduate level teaching, research, and service.

Salary and benefits are competitive and will be commensurate with the qualifications and experience of the applicant.

Applicants with a Ph.D., M.D., or DVM degree and a strong independent publication record should send their CV, a statement of research interests and arrange to have three letters of reference sent to: **Chair, Virology Search Committee, Department of Microbiology, Box 357242 or K357B, University of Washington, 1705 N.E. Pacific Street, Seattle WA 98195. Application deadline: March 1, 2010.**

The University of Washington is an Affirmative Action, Equal Opportunity Employer and is building a culturally diverse faculty. Applications from female and minority candidates are encouraged.

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